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PTO/SB/21 (09-04) Approved for use through 07/31/2006. OMB 0651-0031

linder the Paperwork Reduction Act of 1995, <u>no perso</u>		Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE lection of information unless it displays a valid OMB control number.
	Application Number	10/550,608
TRANSMITTAL	Filing Date	September 26, 2005
FORM	First Named Inventor	Martinez, et al.
	Art Unit	Unassigned
o be used for all correspondence after initial filing)	Examiner Name	Unassigned
	Attorney Docket Number	ABG 3008

Total Number of	Pages in	This Submission			ABG	3006	
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Date	8	128/06		F	Reg. No.	56,794	
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I hereby certify th sufficient postage the date shown be Signature	as first o	rrespondence is b class mail in an en	eing fac velope	csimile transmitted to the USPT0 addressed to: Commissioner for	O or depos Patents, F	sited with the L P.O. Box 1450	Inited States Postal Service with Alexandria, VA 22313-1450 on
Typed or printed	name	Moira An	ders	son	-	Date	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PATENT

IN THE UNITED STATE PATENT AND TRADEMARK OFFICE

plication of: : Martinez et al.

For: : IN VITRO METHOD TO DETECT

BLADDER TRANSITIONAL CELL

CARCINOMA

Serial No. : 10/550,608

Filed : September 26, 2005

Art Unit : Unassigned

Examiner : Unassigned

Attorney Docket No. : ABG 3008

.

Confirmation No. : Unassigned

RENEWED PETITION UNDER 37 C.F.R. § 1.47(a)

Mail Stop PCT Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450

Dear Sir:

As stated in the petition dated April 19, 2006, one of the joint inventors of the above referenced application has refused to join in the application for patent. Therefore, the Applicants hereby renew the petition to make the application on their behalf and the non-signing inventor.

The original Petition filed on April 19, 2006 was dismissed. Therefore, we have filed this renewed petition in response. The petition filed April 19, 2006 was dismissed because English translations of the factual proof exhibits were not provided. As such, we have attached English translations of the communications between the missing inventor and the Assignee's representatives. The translated documents are a true and accurate translation of the documents originally submitted. A recital of the contents of these documents is included with this renewed Petition.

A bona fide attempt to comply with the requirements of 37 C.F.R. § 1.47 has been made as

Application No.: 10/550,608 Attorney Docket No.: ABG 3008

discussed in detail below.

The pertinent facts of the case have been presented in a letter from the Assignee's Foreign Legal Representative attached as Exhibit A. The Assignee and the Assignee's Legal Representative have performed the following steps on the Applicants' behalf in order to contact the non-signing inventor, Miguel Molina Vila:

- 1. On September 29, 2005, the Assignee, PROGENIKA BIOPHARMA, S.A. mailed a copy of the Assignment and Declaration and Power of Attorney to the last known address of the non-signing inventor, along with a copy of the abstract of the PCT application. The mailing is attached as Exhibit B. The non-signing inventor did not reply to the first letter.
- 2. On November 3, 2005, the Assignee, PROGENIKA BIOPHARMA, S.A. mailed a copy of the Assignment and Declaration and Power of Attorney to the last known address of the non-signing inventor, along with copies of the Assignment and Declaration and Power of Attorney signed by all of the other inventors. The mailing is attached as Exhibit C. The non-signing inventor did not reply to the second letter.
- 3. Following the lack of response by the non-signing inventor, the Applicants attempted to locate the inventor through the Spanish equivalent of the personal phone directory or "Yellow Pages" and discovered that the non-signing inventor was not listed. The Applicants attempts are described in an email listed as Exhibit D.
- 4. The Assignee's Legal Representative, ABG PATENTES obtained the email address of the inventor. On February 7, 2006, the ABG PATENTES emailed the non-signing inventor electronic copies of the Assignment and Declaration and Power of Attorney. The non-signing inventor replied through email asking for the best way to sign and return the documents. Thing string of emails is attached as Exhibit E.
- On February 8, 2006, the non-signing inventor wrote an email asking to change the address on the Declaration and Power of Attorney to his new home address without providing the address. The non-signing inventor also asked if he would lose ownership rights in the patent application by signing the assignment. This string of emails is attached as Exhibit F.
- 6. On February 9, 2006, ABG PATENTES responded to the inventor stating that they would change the address in the Declaration and Power of Attorney if provided. Also, ABG PATENTES stated that according to the non-signing inventor's contract signed with Assignee, the non-signing inventor was required to assign all ownership rights in the patent application to the Assignee. A copy of the contract was included with the email. This string of emails is attached as Exhibit G.

Application No.: 10/550,608 Attorney Docket No.: ABG 3008

- 7. The non-signing inventor did not respond to the email dated February 9, 2006.
- 8. ABG PATENTES emailed a reminder to the non-signing inventor on February 15, 2006 and did not receive a response. The email reminder is attached as Exhibit H.
- 9. ABG PATENTES emailed a reminder to the non-signing inventor on February 20, 2006 and did not receive a response. The email reminder is attached as Exhibit I.
- 10. ABG PATENTES emailed a reminder to the non-signing inventor on March 9, 2006 that included copies of the application documents as filed in the U.S.P.T.O., and the assignment documents. The non-signing inventor did not respond to the email of March 9, 2005. The email reminder is attached as Exhibit J.

The last known address of the non-signing inventor is:

Miguel Molina Vila C/ Pintura 1, 5°, 2^a 08035- Barcelona

A bona fide attempt to comply with the requirements of 37 C.F.R. § 1.47(a) has been made as discussed in detail below. The non-signing inventor has refused to join in the signing of the application.

In view of the above, Applicants request that the renewed Petition be granted.

Respectfully submitted,

8/28/06

Date

KRAMER & AMADO, P.C.

Andreas Baltatzis

Reg. No. 56,794



14 JUL 2006

COMMISSIONER FOR PATENTS

JNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450

ALEXANDRIA, VA 22313-1450

WWW.UEDIO.GOV

KRAMER & AMADO, P.C. 1725 DUKE STREET SUITE 240 ALEXANDRIA, VA 22314

In re Application of MARTINEZ et al U.S. Application No.: 10/550,608

PCT Application No.: PCT/EP04/03219

Int. Filing Date: 25 March 2004

Priority Date Claimed: 26 March 2003

Attorney Docket No.: ABG 3008

For: IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL

CARCINOMA

DECISION

This is in response to applicant's "Petition to File on Behalf of Inventor Who Refuses to Join in Application Under 37 C.F.R. §1.47" filed 19 April 2006.

BACKGROUND

On 25 March 2004, applicant filed international application PCT/EP04/03219, which claimed priority of an earlier Spain application filed 26 March 2003. A copy of the international application was communicated to the USPTO from the International Bureau on 07 October 2004. The thirty-month period for paying the basic national fee in the United States expired on 26 September 2005.

On 26 September 2005, applicant filed national stage papers in the United States Designated/Elected Office (DO/EO/US). The submission was accompanied by, *inter alia*, the basic national fee required by 35 U.S.C. 371(c)(1).

On 19 April 2006, applicant filed the present petition under 37 CFR 1.47(a).

On 27 June 2006, the DO/EO/US mailed a Notification of Missing Requirements Under 35 U.S.C. 371 (Form PCT/DO/EO/905), which indicated that an oath or declaration in compliance with 37 CFR 1.497 must be filed.

DISCUSSION

A petition under 37 CFR 1.47(a) must be accompanied by: (1) an oath or declaration by each applicant on his or her own behalf and on behalf of the nonsigning joint inventors, (2) factual proof that the missing joint inventors refuse to join in the application or cannot be reached after diligent effort, (3) the fee set forth in §1.17(i), and (4) the last known addresses of the nonsigning joint inventors.

With regard to item (1) above, applicant has submitted a declaration signed by the available inventors each on his/her own behalf and on behalf of the nonsigning inventor.

With regard to item (2) above, MPEP 409.03(d) states in relevant part,

Where a refusal to sign the application papers is alleged, the circumstances of this refusal must be specified in an affidavit or declaration by the person to whom the refusal was made. Statements by a party not present when an oral refusal is made will not be accepted.

Before a refusal can be alleged, it must be demonstrated that a bona fide attempt was made to present a copy of the application papers (specification, including claims, drawings, and oath or declaration) to the nonsigning inventor for signature. A copy of the application papers should be sent to the last known address of the nonsigning inventor, or, if the nonsigning inventor is represented by counsel, to the address of the nonsigning inventor's attorney.

When there is an express oral refusal, that fact along with the time and place of the refusal must be stated in the affidavit or declaration. When there is an express written refusal, a copy of the document evidencing that refusal must be made part of the affidavit or declaration.

When it is concluded by the 37 CFR 1.47 applicant that a nonsigning inventor's conduct constitutes a refusal, all facts upon which that conclusion is based should be stated in the affidavit or declaration. If there is documentary evidence to support facts alleged in the affidavit or declaration, such evidence should be submitted. Whenever a nonsigning inventor gives a reason for refusing to sign the application oath or declaration, that reason should be stated in the affidavit or declaration.

The petition states that joint inventor Miguel Molina Vila refuses to sign the application papers. Although the petition states that a bona fide attempt was made to present a copy of the application papers to Miguel Molina Vila for signature via electronic mail on 09 March 2006, an English language translation of the electronic mail message has not been provided. Similarly, English language translations of the rest of the electronic mail correspondence with Miguel Molina Vila have not been provided. Thus, it would not be reasonable to conclude at the present time that Miguel Molina Vila refuses to join in the application.

With regard to item (3) above, applicant has provided the requisite petition fee.

With regard to item (4) above, the petition states the last known address of the nonsigning inventor.

Application Number: 10/2 ,608

CONCLUSION

For the reasons above, the petition under 37 CFR 1.47(a) is <u>DISMISSED</u> without prejudice.

If reconsideration on the merits of this petition is desired, a proper response must be filed within TWO (2) MONTHS from the mail date of this decision. Extensions of time are available under 37 CFR 1.136(a). Any reconsideration request should include a cover letter entitled "Renewed Petition Under 37 CFR 1.47(a)". No additional petition fee is required.

Please direct further correspondence with respect to this matter to Mail Stop PCT, Commissioner for Patents, Office of PCT Legal Administration, P.O. Box 1450, Alexandria, Virginia 22313-1450, with the contents of the letter marked to the attention of the Office of PCT Legal Administration.

Bryan Tung

PCT Legal Examiner

PCT Legal Office

Telephone: 571-272-3303 Facsimile: 571-273-0459



RECEIVED



MAR 0 9 2006

ARIAS , BERNARDO & GONZÁLEZ Asesoría y Agencia de la Propiedad Industitationer & Amado, P.C. Intellectual Property

KRAMER & AMADO, P.C. 1725 Duke Street, Suite 240

Atn.:Arlir Amado

Alexandria, Virginia 22314 **United States**

Via Facsimile Confirmation by mail

Our ref.: P1121USPC Your ref.: ABG 3008

Madrid, March 3, 2006

Patent Application in United States No. 10/550,608 with title "IN Re: VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA", in the name of PROGENIKA BIOPHARMA,

Dear Sirs,

Further to your mail dated January 31, 2006, please be informed that in order to get the signature of the inventor (Miguel Angel Molina), the following steps have been performed:

- First of all, the Applicant sent the documentation two or three times to the last known address of the inventor, but there was no answer. Then, the applicant tried to locate him per "yellow pages" of the Spanish Telephone Company, but there was no input under his name.
- Afterwards, ABG Patentes got the e-mail address of the inventor by chance (through an indirect personal contact).
- On February 7, 2005, ABG Patentes sent Miguel Angel Molina via e-mail the documents of "Assignment" and "Declaration and Power of Attorney". He answered to this e-mail asking how is the better way to return us these documents once signed. We answered this question thinking that he was ready to cooperate.
- On February 8, 2006, he wrote again asking whether it was possible to change the address of the document of "Declaration and Power of Attorney" to his home address and, also, that if the signature of the document of "Assignment" meant to loose his rights over this patent

Juan Arias M. Sc. Chemistry

PARTNERS

European Patent Attorney Spanish Patent & Trademark Attorney Francisco Bernardo

M. Sc. Chemistry European Patent Attorney, CEIPI Vicente González

, M. Sc. Chemistry & Biotechnology Fernando Prieto B. Sc. Electronic Engineering, ICAI

PATENT ADVISERS Gert-Jan Baas

M. Sc. Elect. Engineering (Telecom.) European Patent Attorney Cristina Zabalo

M. Sc. Chemistry Almudena Fernández Ph. D. Chemistry Miquel Lorca M. Sc. Chemistry Esther Martinez

M. Sc. Biology María José Carrascosa

Ph. D. Biology

TRADEMARKS

Christine Weimann Attorney-at-Law Spanish Patent & Trademark Attorney Community Trademark & Design Attorney

HEAD OF FORMALITIES Cecilia Ranilla M. Sc. Business Administration

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M. Zardi & Co. S.A. Vía G.B. Pioda, 6 CH-6900 Lugano (Switzerland) www.zardi.ch

lomo 19,273, ubro 0, Folic 112, Sección 8. Hoja M-337602 ~ Inscripción 1ª - AilF B-837-59737



- On February 9, 2006, we answered to his questions saying that we would change his address in the document of "Declaration and Power of Attorney", and that if he signed the document he would loose indeed, any kind of rights over the patent. We continued by saying that according to the Spanish Patent Law, and according to the contract he signed with the Applicant, the inventions made during his stay in the company are considered to belong to the company he works or worked for.
- After our last e-mail (February 9, 2006), we sent him two reminders about this matter, one on February 15, 2006 and the other one on February 20, 2006, but the inventor has not answered yet. Moreover, we believe the inventor will never answer back. Unfortunately, we could only get his e-mail address, not his home or work address.

This is the present situation for this case. Therefore, we would appreciate if you could inform us what would be the following step with respect to the filing of the Assignment" and "Declaration and Power of Attorney" before the USPTO

Best regards,

Juan Arias Sanz

European Patent Attorney

ABG Patentes, S.L.



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

As a below named inventor	I hereb	v declare that:
---------------------------	---------	-----------------

My residence/post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56:

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: NO: X
Spain	P200300708	03/26/2003	YES: X NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE	

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)
	· .	•

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Power of Attorney:

Tower of Attorney.	
As a named inventor, I hereby appoint the attorney(s) and/or a	
application and transact all business in the Patent and Tradem	
Send correspondence to:	Direct telephone calls to:
Arlir M. Amado	
Kramer & Amado, P.C.	Arlir M. Amado
1725 Duke Street, Suite 240	(703) 519-9801
Alexandria, VA 22314	
Phone: (703) 519-9801	14
Fax: (703) 519-9802	
I hereby declare that all statements made herein of my ow	
information and belief are believed to be true; and further the	
willful false statements and the like so made are punishable by	
18 of the United States Code and that such willful false statem	ents may jeopardize the validity of the application or any
patent issued thereon.	
Full Name of Inventor: Antonio Martínez Martínez	Citizenship: Spain -
ייי אין אין אין אין אין אין אין אין אין	Elici and Dot I / E and O DEDIO AV
Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea	- Edificio 801 - B 2º planta, E-48160 DERIO – Vizcaya,
Spain	
Post Office Address: Same	
Fost Office Addless. Same	
	24.0d. 25-5
Inventor's Signature	Date
	·
Full Name of Inventor: Laureano Simón Buela	Citizenship: Spain
Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea	- Edificio 801 - B 2ª planta, E-48160 DERIO - Vizcaya,
Spain	
Post Office Address: Same	
	24.04.205
	24.04.633
Inventor Signature	Date
Full Name of Inventor: Simon Santa Cruz	Citizenship: Great Britain
Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea	- Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya,
<u>Spain</u>	•
Dest Office Additions for the	
Post Office Address: Same	
	24.0ct. 2005
Inventor's Construe	
Inventor's Signature	Date

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: María Pilar Sáenz Jiménez	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bidea</u> <u>Spain</u>	- Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya,
Post Office Address: Same	
Inventor's Signature	24/10/2005 Date
Full Name of Inventor: Corina Junquera Sánchez-Vallejo	Citizenship: Spain
Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea Spain	- Editicio 801 - B 2 pianta, E-48100 DERIO – Vizcaya,
Post Office Address: Same	
Conne Jurguera	24.00 . 2.5
Inventor's Signature	Date
Full Name of Inventor: <u>José Javier Gómez Román</u>	Citizenship: <u>Spain</u>
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> <u>Spain</u>	VALDECILLA, Avda, Valdecilla s/nE-39008 Santander,
Post Office Address: Same	
	24.0d.2.5
Inventor's Signature	Date
Full Name of Inventor: <u>Jorge Cuevas González</u>	Citizenship: Spain
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> <u>Spain</u>	/ALDECILLA, Avda. Valdecilla s/nE-39008 Santander,
Post Office Address: Same	
Luciac	24.0d. 2=5
Inventor's Signature	Date

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: Miguel Molina Vila	Citizenship: Spain
Residence: C/ Pintura 1, 5° 2ª. E-08035 Barcelona, Spain	
Post Office Address: Same	
	•
Inventor's Signature	Date

Dear Dr. Molina:

You appear as an inventor for regenika Biopharma, SA patent application No. WO2004085676. To confirm your acceptance in the application United States Patent process, it is necessary to obtain your signature for the attached documents (it is necessary to sign in front of a witness for the assignment document) and mail them to the following address:

Laureno Simon Progenika biopharma, SA Parque tecnologice de Vuzcaya 801-B 48160, Derio, Vizcaya

We appreciate your help in this matter,

Laureno Simon.

Progenika biopharma, SA



COTTEON

Y Telégrafos

BARRA-KOBERAKO

GUNEA

BARRA-KOBERAKO

BARRA-KOBERA

BARRA-KOBERAKO

BARRA-KOBERAKO

BARRA-KOBERAKO

BARRA-KOBERAKO

INFORMACIÓN 902 197 197

PROGENIKA S.A.

Edificio 801 . Parque Tecnológico de Zamudio

4**8160 Derio . Spain** Phone: +34 94 406 45 25 Fax: +34 94 406 45 26



D. Miguel Ángel Molina Vila.

DNI: 33895291F

C/ Pintura 1, 5° 2°. 08035 Barcelona



Usted figura como inventor en la solicitud de patente de Progenika biopharma, SA. WO2004085676. Para confirmar su aceptación en el proceso de solicitud en la United States Patent Office, es necesario que firme los documentos que se adjuntan (El documento Assignment es necesario que lo firme adicionalmente un testigo) y los envie a la siguiente dirección:

Laureano Simón. Progenika biopharma, SA Parque Tecnológico de Vizcaya. 801-B. 48160, Derio, Vizcaya.

Agradeciéndole su colaboración, le saluda atentamente,

Laureano Simon.

Progenika biopharma, SA

Assignment	of Patent Application
María Pilar Sáenz Jiménez, Miguel Mol Javier Gómez Román and Jorge Cuevas invented certain new and useful improve DETECT BLADDER TRANSITIONAL (] for which an application for a United Sta	
I for which an application for a United Sta	ites ratent was executed on, and
address is Parque Tecnológico de Zamud	S.A., herein referred to as assignee, whose post office io, Ibaizabal Bidea - Edificio 801 - B 2 ^a plantaE-ous of acquiring the entire right, title and interest in
acknowledged, and other good and valuable do sell, assign and transfer unto said assigned the United States and all countries throug continuations in whole or in part, substextensions thereof, and the entire right, title be granted therefor in the United States and divisions, renewals, continuations in who prolongations and extensions thereof. we Patents and Trademarks to issue said Unite title, and interest in and to the same, for its slegal representatives, to the full end of the and entirely as the same would have been here	um of ten dollars (\$10.00), the receipt whereof is a consideration, we, the applicants, by these presents be the full and exclusive right to the said invention in ghout the world including any divisions, renewals, titutions, conversions, reissues, prolongations and and interest in and to any and all Patents which may ad all countries throughout the world including any alle or in part, substitutions, conversions, reissues, hereby authorize and request the Commissioner of ad States Patent to said assignee, of the entire right, sole use and behoof; and for the use and behoof of its term for which said Patent may be granted, as fully all by us had this assignment and sale not been made.
document any identification which may be transferred under the rules of the United Spurposes.	necessary or desired to reference the property being States Patent and Trademark Office for recordation
EXECUTED THIS day of, 20	_, at
*	
Antonio Martínez Martínez	Date
Witness	

Assign	ment of Patent Application		
Laureano Simón Buela	Date		
			· ,
Witness			
	•		
Simón Santa Cruz	Date		
Simon Santa Cluz	Date		
Witness			
María Pilar Sáenz Jiménez	Date		
			٠
Witness			
witness			
Corina Junquera Sánchez-Vallejo	Date		
Witness		•	
José Javier Gómez Román	Date	· · · · · · · · · · · · · · · · · · ·	
Witness			
I 0 0 1	D /		
Jorge Cuevas González	Date		
Witness			

	Assignment of Patent Application	
Miguel Molina Vila	Date	·



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on ______ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: X NO:
			YES: NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Power of Attorney:

As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to: Arlir M. Amado

respondence to:

Amado

Direct telephone calls to:

Kramer & Amado, P.C. 1725 Duke Street, Suite 240

Arlir M. Amado (703) 519-9801

Alexandria, VA 22314 Phone: (703) 519-9801 Fax: (703) 519-9802

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal</u> <u>Spain</u>	Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya
Post Office Address: Same	
Inventor's Signature	Date
Full Name of Inventor: <u>Laureano Simón Buela</u>	Citizenship: Spain
Residence: Parque Tecnológico de Zamudio, Ibaizabal Spain Post Office Address: Same	Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO — Vizcaya
Inventor's Signature	Date
Full Name of Inventor: Simon Santa Cruz	Citizenship: Great Britain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal)</u> S <u>pain</u>	Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya
Post Office Address: Same	
Inventor's Signature	Date

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: María Pilar Sáenz Jiménez	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bidez</u> Spain	ea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya
Post Office Address: Same	
Inventor's Signature	Date
Full Name of Inventor: Corina Junquera Sánchez-Vallejo	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bidea</u> <u>Spain</u>	a - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya.
Post Office Address: Same	
Inventor's Signature	Date
Full Name of Inventor: <u>José Javier Gómez Román</u>	Citizenship: Spain
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> S <u>pain</u>	VALDECILLA, Avda. Valdecilla s/nE-39008 Santander,
Post Office Address: Same	
<u>.</u>	
Inventor's Signature	Date
Full Name of Inventor: <u>Jorge Cuevas González</u>	Citizenship: Spain
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> Spain	VALDECILLA, Avda. Valdecilla s/nE-39008 Santander,
Post Office Address: Same	
nventor's Signature	Date



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

PATENT APPLICATION

Full Name of Inventor: Miguel Molina Vila	Citizenship: Spain
Residence: C/ Pintura 1, 5° 2ª. E-08035 Barcelona, Spain	
Post Office Address: Same	
*	
Inventor's Signature	Date

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

Patent number:

WO2004085676

Publication date:

2004-10-07

Aug 88 July 8

MARTINEZ MARTINEZ ANTONIO (ES); SIMON BUELA LAUREANO (ES); SANTA CRUZ SIMON (ES); SAENZ JIMENEZ MARIA PILAR (ES); MOLINA VILA MIGUEL (ES); JUNQUERA SANCHEZ-VALLEJO CORIN (ES); GOMEZ ROMAN JOSE JAVIER (ES); CUEVAS

GOMEZ ROMAN JOSE JAVIER

GONZALEZ JORGE (ES)

MEDPLANT GENETICS S L (ES);; MARTINEZ MARTINEZ ANTONIO (ES);; SIMON BUELA

LAUREANO (ES);; SANTA CRUZ SIMON (ES);; SAENZ JIMENEZ MARIA PILAR (ES);; MOLINA VILA MIGUEL (ES);; JUNQUERA SANCHEZ-VALLEJO CORIN (ES);; GOMEZ ROMAN JOSE JAVIER (ES);; CUEVAS

GONZALEZ JORGE (ES)

Classification:

- international:

C12Q1/68; G01N33/574

- european:

G01N33/574C

Application number: WO2004EP03219 20040325 Priority number(s): ES20030000708 20030326

Cited documents:



WO0068424 WO0210285 XP00218167 XP00103099

Report a data error he

Abstract of WO2004085676

The present invention refers to an in vitro method to detect a bladder transitional cell carcinoma, in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with this cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against this cancer in order to develop new medicinal products, and also agents that inhibit the expression and/or activity of the FGFR3 protein and/or the effects of this expression.

Data supplied from the esp@cenet database - Worldwide

Dear Dr. Molina:

You appear as an inventor for Progenika Biopharma, SA patent application No. WO2004085676. To confirm your acceptance in the application United States Patent process, it is necessary to obtain your signature for the attached documents (it is necessary to sign in front of a witness for the assignment document) and mail them to the following address:

Laureno Simon Progenika biopharma, SA Parque tecnologice de Vuzcaya 801-B 48160, Derio, Vizcaya

We appreciate your help in this matter,

Laureno Simon.

Progenika biopharma, SA

C/ PINTURA Población Herria 73A Carta Certificada ☑Carta □Paquete Postal □Impreso □Paquete Azyl Fecha:03/11/2005 ਲੈਂਡੋਂ Peso: 64 gr. Hora:13:21 Importe: 2,48 € Sello de fechas o validación mecánica Data-zigilua, edo makinaz baliozkotua CAUREDM

INFORMACIÓN 902 197 197

PROGENIKA S.A.
Edificio 801 . Parque Tecnológico de Zamudio
48160 . Spain
Phono: 34.94.406.45.25

Phone: +34 94 406 45 2 Fax: +34 94 406 45 26 www.progenika.com



D. Miguel Ángel Molina Vila.

DNI: 33895291F

C/ Pintura 1, 5° 2°. 08035 Barcelona

Estimado Dr. Molina:

Usted figura como inventor en la solicitud de patente de Progenika biopharma, SA. WO2004085676. Para confirmar su aceptación en el proceso de solicitud en la United States Patent Office, es necesario que firme los documentos que se adjuntan (El documento Assignment es necesario que lo firme adicionalmente un testigo) y los envíe a la siguiente dirección:

Laureano Simón.

Progenika biopharma, SA

Parque Tecnológico de Vizcaya. 801-B.
48160, Derio, Vizcaya.

Agradeciéndole su colaboración, le saluda atentamente,

Laureano Simón. Progenika biopharma, SA

Assignment of Patent Application
Whereas, we, Antonio Martínez Martínez, Laureano Simón Buela, Simon Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González, hereafter referred to as applicants, have invented certain new and useful improvements relating to an IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA [] for which an application for a United States patent was filed on, and, and
Whereas, PROGENIKA BIOPHARMA, S.A., herein referred to as assignee, whose post office address is Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª plantaE-48160 - DERIO - Vizcaya, Spain, is desirous of acquiring the entire right, title and interest in the same:
Now, therefore, in consideration of the sum of ten dollars (\$10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.
The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes. EXECUTED THIS day of, 20, at
Antonio Martínez Martínez Date
Witness

Assign	ment of Patent A	pplication	
Laureano Simón Buela	Date		
Witness		·	
· .	•		
Simón Santa Cruz	Date		
Witness			
María Pilar Sáenz Jiménez	Date		
Witness			
Corina Junquera Sánchez-Vallejo	Date		
Witness			
José Javier Gómez Román	Date	· .	
Witness			
Jorge Cuevas González	Date		
Witness			
	Page 2 of 3		

	Assignment of Patent Applic	cation
	•	
Miguel Molina Vila	Date	

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

the specification of which is attached hereto unless the following box is checked:

(X)	was filed	on March	<u>25, 2004</u>	as PCT	International	Application	Number	PCT/EP04/003219	and	was
amended on				_ (if app	licable).					

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	
PCT	PCT/EP04/003219	03/25/2004	YES: X NO:
			YES: NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)
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DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER: 30868**

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٨	_	_				:	• • •		٠.	_

Fax: (703) 519-9802

As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to: Arlir M. Amado Kramer & Amado, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Phone: (703) 519-9801

Arlir M. Amado (703) 519-9801

Direct telephone calls to:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez	Citizenship: Spain		
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal</u> <u>Spain</u>	Bidea - Edificio 801 - B 2º planta, E-48160 DERIO - Vizcaya		
Post Office Address: Same			
Inventor's Signature	Date		
Full Name of Inventor: Laureano Simón Buela	Citizenship: Spain		
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal</u> <u>Spain</u> Post Office Address: <u>Same</u>	Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya		
Inventor's Signature	Date		
Full Name of Inventor: Simon Santa Cruz	Citizenship: Great Britain		
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal</u> <u>Spain</u>	Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO - Vizcaya		
Post Office Address: Same			
Inventor's Signature	Date		

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: María Pilar Sáenz Jiménez	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bides</u> <u>Spain</u>	a - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya
Post Office Address: Same	
	·
Inventor's Signature	Date
Full Name of Inventor: Corina Junquera Sánchez-Vallejo	Citizenship: Spain
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bides Spain</u>	a - Edificio 801 - B 2ª planta, E-48160 DERIO Vizcaya
Post Office Address: Same	
Inventor's Signature	Date
Full Name of Inventor: José Javier Gómez Román	Citizenship: Spain
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE Spain</u>	VALDECILLA, Avda. Valdecilla s/nE-39008 Santander
Post Office Address: Same	
Inventor's Signature	Date
Full Name of Inventor: Jorge Cuevas González	Citizenship: Spain
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE Spain</u>	VALDECILLA, Avda. Valdecilla s/nE-39008 Santander
Post Office Address: Same	
Inventor's Signature	Date



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: Miguel Molina Vila	Citizenship: Spain	
Residence: C/ Pintura 1, 5° 2°. E-08035 Barcelona, Spain		
Post Office Address: Same		_
Inventor's Signature	Date	_

Beatriz Rodera [ABG PATENTES]

From: Laureano Simon [lsimon@progenika.com]

Sent: Wednesday, February 1, 2006 14:01 To: Beatriz Rodera [ABG PATENTES] CC: Juan Arias: psaenz@proteomika.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Beatriz,

Pursuant to your instructions, we have sent documentation to Miguel Angel Molina Vila which he needs to sign, via certified mail, and two separate times every 15 days; both letters have not been returned.

The address used is the latest one showing in our company database.

We have not located his information by searching the internet.

After consulting 11818, there is no phone number found in the city of Barcelona (the city in where he resides), neither is his name found within the province.

Greetings,

Laureano.

From: Beatriz Rodera [ABG PATENTES]

Sent: Wednesday, February 1, 2006 11:28AM To: Laureno Simon" < lsimon@progenika.com> CC: Juan Arias < jarias@abgpatentes.com>

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Simon,

Regarding the application mentioned above, we inform you that due to the constant signature refusal of Miguel Angel Molina Vila for the "Power of Attorney" and the "Assignment" documents, our correspondents in U.S. need the determined information in order to prepare the documents for filing before the Unites States Patent and Trademark Office. (USPTO).

Therefore, we will need the following information confirmed and that, in your case, to contribute the following documentation:

- 1. We understand that there was no response from the inventor, therefore, there was not any verbal or written communication stating negative to sign the documents. Please to confirm this point.
- 2. It is important to have certainty that the documentation were sent to the inventor's last known address. Consequently, it is necessary to confirm that this was done the correct way, and to contribute any documentation that proofs that Progenika has confirmed the last known address by having the Human Resources Department search in the phone book, internet or any other method.

We look forward to your comments,

Greetings,

Beatriz Rodera Tobal Formalities Department

ABG PATENTES
Orense 68, 7a Planta
28020 Madrid
(SPAIN)

Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes

De: Laureano Simon [Isimon@progenika.com]

Enviado: miércoles, 01 de febrero de 2006 14:01

Para: Beatriz Rodera [ABG PATENTES]

CC: Juan Arias; psaenz@proteomika.com

Asunto: Re: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Beatriz:

Siguiendo vuestras instrucciones, hemos enviado la documentación a firmar a Miguel Angel Molina Vila, por correo certificado, 2 veces separadas por 15 días; las cartas nos han sido devueltas y os hemos enviado a vosotros los sobres devueltos (sin abrir).

La dirección es la última que figura en la base de datos de la empresa.

No le hemos localizado haciendo búsquedas en internet.

Tras consulta al 11818, No hay ningún abonado telefónico en Barcelona (ciudad en la que residía), ni en la provincia con su nombre.

Saludos.

Laureano.

Laureano Simon.

Progenika biopharma, S.A.

Parque tecnológico de Zamudio. 801.

48160, Derio (Bilbao). Vizcaya. Spain.

Tel: +34 94 4064525 Fax: +34 94 4064526 www.progenika.com

Advertencia: Este correo electrónico contiene información privada y estrictamente confidencial. Si usted no es el destinatario del presente mensaje, no está autorizado a leerlo, retenerlo o difundirlo.

Warning: This e-mail is privileged, confidential and contains private information. Any reading, retention, distribution or copying of this communication by any person other than its intended recipient is prohibited.

---- Original Message -----

From: Beatriz Rodera [ABG PATENTES]

To: 'Laureano Simon' Cc: Juan Arias

Sent: Wednesday, February 01, 2006 11:28 AM

Subject: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA

BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación con la solicitud de patente de la referencia, le informamos que debido a la negativa de D. Miguel Ángel Molina Vila a firmar los documentos de "*Power of Attorney*" y de "*Assignment*", nuestros corresponsales en USA necesitan determinada información para preparar la documentación necesaria para presentar un escrito ante la Oficina Norteamericana de Patentes (USPTO).

Necesitaríamos, por tanto, que nos confirmen la siguiente información y que, en su caso, aporten la

De: Laureano Simon [Isimon@progenika.com]

Enviado: miércoles, 01 de febrero de 2006 14:01

Para: Beatriz Rodera [ABG PATENTES]

CC: Juan Arias; psaenz@proteomika.com

Asunto: Re: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Beatriz:

Siguiendo vuestras instrucciones, hemos enviado la documentación a firmar a Miguel Angel Molina Vila, por correo certificado, 2 veces separadas por 15 días; las cartas nos han sido devueltas y os hemos enviado a vosotros los sobres devueltos (sin abrir).

La dirección es la última que figura en la base de datos de la empresa.

No le hemos localizado haciendo búsquedas en internet.

Tras consulta al 11818, No hay ningún abonado telefónico en Barcelona (ciudad en la que residía), ni en la provincia con su nombre.

Saludos.

Laureano.

Laureano Simon.

Progenika biopharma, S.A.

Parque tecnológico de Zamudio. 801. 48160, Derio (Bilbao). Vizcaya. Spain.

Tel: +34 94 4064525

Fax: +34 94 4064526 www.progenika.com

Advertencia: Este correo electrónico contiene información privada y estrictamente confidencial. Si usted no es el destinatario del presente mensaje, no está autorizado a leerlo, retenerlo o difundirlo.

Warning: This e-mail is privileged, confidential and contains private information. Any reading, retention, distribution or copying of this communication by any person other than its intended recipient is prohibited.

---- Original Message -----

From: Beatriz Rodera [ABG PATENTES]

To: 'Laureano Simon' Cc: Juan Arias

Sent: Wednesday, February 01, 2006 11:28 AM

Subject: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA

BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación con la solicitud de patente de la referencia, le informamos que debido a la negativa de D. Miguel Ángel Molina Vila a firmar los documentos de "*Power of Attorney*" y de "*Assignment*", nuestros corresponsales en USA necesitan determinada información para preparar la documentación necesaria para presentar un escrito ante la Oficina Norteamericana de Patentes (USPTO).

Necesitaríamos, por tanto, que nos confirmen la siguiente información y que, en su caso, aporten la

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 16:10

To: miguelamol@hotmail.com

cc: Juan Arias (jarias@abgpatentes.com)

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

Thank you for your prompt response.

It will be sufficient if you could send us the documents via mail, or if possible certified, since we will need the documents to have your original signature as well as the original signature of a witness.

Greetings,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

From: Miguel Molina [mailto: miguelamol@hotmail.com]

Sent: Tuesday, February 7, 2006 15:07

To: brodera@abgpatentes.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mrs. Rodera

Thank you for sending me the documents, I will sign them this week. Nevertheless, I have a question: what is the procedure to return these? Regular mail, fax or via e-mail as an attachment (PDF format)?

Sincerely,

Miguel A. Molina

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 10:57:04 + 0100

To: Miguel Molina [mailto: miguelamol@hotmail.com]

CC: Juan Arias <jarias@abgpatentes.com>, "Laureno Simon" <lsimon@progenika.com>

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Molina:

Pursuant to D. Juan Arias instructions, we would like to inform you that the above mentioned patent application is currently in the process of being filed in Unites States. D. Gregorio Valencia has provided us with your e-mail address in order to contact you and be able to provide you with the "Declaration and Power of Attorney" and "Assignment" documents, consequently, please proceed to sign and date both documents which are necessary in the filing process for the mentioned country and in this fashion we can file the application before the United States Patent and Trademark Office, as is the Patent Law establishes in Article 18.2 (11/1986).

For the "Assignment" document we will also need a signature from a witness for validity purposes.

Thank you with your help in this matter,

Sincerely,

Beatriz Rodera Tobal Formalities Department

ABG PATENTES
Orense 68, 7a Planta
28020 Madrid
(SPAIN)

From: Miguel Molina [mailto: miguelamol@hotmail.com]

Sent: Tuesday, February 7, 2006 15:07

To: brodera@abgpatentes.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mrs. Rodera

Thank you for sending me the documents, I will sign them this week. Nevertheless, I have a question: what is the procedure to return these? Regular mail, fax or via e-mail as an attachment (PDF format)?

Sincerely,

Miguel A. Molina

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 10:57:04 + 0100

To: Miguel Molina [mailto: miguelamol@hotmail.com]

CC: Juan Arias < jarias@abgpatentes.com>, "Laureno Simon" < lsimon@progenika.com>

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Molina:

Pursuant to D. Juan Arias instructions, we would like to inform you that the above mentioned patent application is currently in the process of being filed in Unites States. D. Gregorio Valencia has provided us with your e-mail address in order to contact you and be able to provide you with the "Declaration and Power of Attorney" and "Assignment" documents, consequently, please proceed to sign and date both documents which are necessary in the filing process for the mentioned country and in this fashion we can file the application before the United States Patent and Trademark Office, as is the Patent Law establishes in Article 18.2 (11/1986).

For the "Assignment" document we will also need a signature from a witness for validity purposes.

Thank you with your help in this matter,

Sincerely,

Beatriz Rodera TobalFormalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN)

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 10:57:

To: Miguel Molina [mailto: miguelamol@hotmail.com]

CC: Juan Arias <jarias@abgpatentes.com>, "Laureno Simon" <lsimon@progenika.com>

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Molina:

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For the "Assignment" document we will also need a signature from a witness for validity purposes.

Thank you with your help in this matter,

Sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES
Orense 68, 7a Planta
28020 Madrid
(SPAIN)

From: Juan Arias [jarias@abgpatentes.com]

Sent: Tuesday, February 7, 2006 10:06

To: Miguel Molina [mailto: miguelamol@hotmail.com];gvpqbp@iiqab.csic.es

CC: genqbp@yahoo.es; Beatriz Rodera [ABG PATENTES]

Subject: Miguel Angel Molina Contact Information

Dear Mr. Molina:

Thank you for your e-mail.

Shortly you will receive an e-mail from Beatriz Rodera (ABG patentes) in which she will explain in detail the reason why we have tried to get in contact with you (your signature is needed in a document).

Cordially,

Juan Arias Sanz

Partner

M.Sc (Chemistry)
Spanish Patent Agent/ European
Patent Attorney

ABG PATENTES

Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 jarias@abgpatentes.com www.abgpatentes.com

From: Miguel Molina [miguelamol@hotmail.com]

Sent: Tuesday, February 7, 2006 9:32

To: gvpqbp@iiqab.csic.es; jarias@abgpatentes.com

CC: genqbp@yahoo.es

Subject: Miguel Angel Molina Contact Information

Dear Mr. Arias

Dr. Gregorio Valencia and Dr. Gemma Espuña have let me know that you wished to get in contact with me. You can find me at this e-mail address.

Sincerely,

Miguel Molina

From: Gregorio Valencia <gvpqbp@iiqab.csic.es>

Sent: Monday, February 6, 2006 18:42:48

To: gvpqbp@iiqab.csic.es; jarias@abgpatentes.com CC: genqbp@yahoo.es; Miguelamol@hotmail.com Subject: Miguel Angel Molina Contact Information

Dear Juan,

In fact, as you can see in this message, Gemma Espuña continues to keep in touch with Miguel Angel Molina. You can find Miguel's e-mail address in Gemma's Header.

Hugs, Gregorio

De: Mig

Miguel Molina [miguelamol@hotmail.com]

Enviado: martes, 07 de febrero de 2006 15:07

Para:

brodera@abgpatentes.com

Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera

Muchas gracias por enviar los documentos, los firmaré esta misma semana. Me queda sin embargo una duda: ¿qué procedimiento debo seguir para devolverlos? ¿correo ordinario, fax o adjunto a mensaje de correo electrónico (en formato pdf)?

Atentamente,

Miguel A Molina

From: "Beatriz Rodera [ABG PATENTES]"

**brodera@abgpatentes.com

To: <miquelamol@hotmail.com>

CC: "Juan Arias" <jarias@abgpatentes.com>, "'Laureano Simon'" <lsimon@progenika.com> Subject: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Date: Tue, 7 Feb 2006 10:57:04 +0100

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Molina:

En relación a la solicitud de patente de la referencia y según instrucciones de D. Juan Arias, le informamos que nos estamos ocupando de la tramitación de dicha solicitud en Estados Unidos. D. Gregorio Valencia nos ha proporcionado su dirección de e-mail para contactar con Vd. y así poder enviarle los documentos de "Declaration and Power of Attorney" y "Assignment" para que por favor proceda a fechar y firmar ambos documentos necesarios para la tramitación en dicho país y de esta manera poder presentarlos ante la Oficina de Patentes de Estados Unidos (USPTO), tal y como establece el Articulo 18.2 de la Ley de Patentes (11/1986).

Para el caso del documento de "Assignment" se necesita también la firma de un testigo con el fin de dar validez a este documento.

Muchas gracias por su colaboración.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN) Tel.: +34 91 417 1300 Fax: +34 91 417 1301

brodera@abgpatentes.com http://www.abgpatentes.com ><< Assignment-P1121USPC.doc >>

><< DeclarationandPowerofAttorneyfinal-P1121USPC.doc >>

De:

Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Enviado: martes, 07 de febrero de 2006 10:57

Para:

'miguelamol@hotmail.com'

CC:

Juan Arias (jarias@abgpatentes.com); 'Laureano Simon'

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

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Muchas gracias por su colaboración.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Assignment	of Patent Application
María Pilar Sáenz Jiménez, Miguel Mod Javier Gómez Román and Jorge Cuevas invented certain new and useful improve DETECT BLADDER TRANSITIONAL [] for which an application for a United Sta	
address is Parque Tecnológico de Zamud	S.A., herein referred to as assignee, whose post office lio, Ibaizabal Bidea - Edificio 801 - A 2 ^a plantaE-rous of acquiring the entire right, title and interest in
acknowledged, and other good and valuable do sell, assign and transfer unto said assigne the United States and all countries throug continuations in whole or in part, subsextensions thereof, and the entire right, title be granted therefor in the United States and divisions, renewals, continuations in who prolongations and extensions thereof. we Patents and Trademarks to issue said Unite title, and interest in and to the same, for its slegal representatives, to the full end of the	um of ten dollars (\$10.00), the receipt whereof is a consideration, we, the applicants, by these presents see the full and exclusive right to the said invention in ghout the world including any divisions, renewals, titutions, conversions, reissues, prolongations and and interest in and to any and all Patents which may and all countries throughout the world including any olle or in part, substitutions, conversions, reissues, hereby authorize and request the Commissioner of ed States Patent to said assignee, of the entire right, sole use and behoof; and for the use and behoof of its term for which said Patent may be granted, as fully eld by us had this assignment and sale not been made.
document any identification which may be	Kramer and Amado, P.C. the power to insert on this necessary or desired to reference the property being States Patent and Trademark Office for recordation, at
Antonio Martínez Martínez	Date
Witness	

Assign	ment of Patent Application	
Laureano Simón Buela	Date	
Witness		
Simón Santa Cruz	Date	
Witness	•	
María Pilar Sáenz Jiménez	Date	
Witness	•	
Corina Junquera Sánchez-Vallejo	Date	<u> </u>
Witness		
José Javier Gómez Román	Date	
Witness		
Jorge Cuevas González	Date	
Witness		

	Assignment of Patent Application		
N.C I N.C. II N.C			
Miguel Molina Vila	Date		

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

As	a	below	named	inventor,	I	hereby	v declare	that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on ______ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: NO: X
Spain	P200300708	03/26/2003	YES: X NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Power of Attorney:

As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to: Arlir M. Amado Kramer & Amado, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Phone: (703) 519-9801

Fax: (703) 519-9802

Arlir M. Amado

(703) 519-9801

Direct telephone calls to:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez	Citizenship: Spain		
Residence: Parque Tecnológico de Zamudio, Ibaizabal Spain	Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO - Vizcaya		
Post Office Address: Same			
Inventor's Signature	Date		
Full Name of Inventor: <u>Laureano Simón Buela</u>	Citizenship: Spain		
Residence: Parque Tecnológico de Zamudio, Ibaizabal Spain	Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya		
Post Office Address: Same			
Inventor's Signature	Date		
Full Name of Inventor: Simón Santa Cruz	Citizenship: Spain		
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal</u> <u>Spain</u>	Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO — Vizcaya,		
Post Office Address: Same			
Inventor's Signature	Date		

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: María Pilar Sáenz Jiménez	Citizenship: Spain		
Residence: Edificio 801A. Parque Tecnológico de Zamudio,	E-48160 Derio, Spain		
Post Office Address: Same			
Inventor's Signature	Date .		
Full Name of Inventor: Corina Junquera Sánchez-Vallejo	Citizenship: Spain		
Residence: <u>Parque Tecnológico de Zamudio, Ibaizabal Bidea</u> S <u>pain</u>	- Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya,		
Post Office Address: <u>Same</u>			
Inventor's Signature	Date		
Full Name of Inventor: <u>José Javier Gómez Román</u>	Citizenship: Spain		
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> <u>Spain</u>	VALDECILLA, Avda. Valdecilla s/n E-39008 Santander,		
Post Office Address: Same			
Inventor's Signature	Date		
Full Name of Inventor: <u>Jorge Cuevas González</u>	Citizenship: Spain		
Residence: <u>HOSPITAL UNIVERSITARIO MARQUÉS DE V</u> Spain	VALDECILLA, Avda. Valdecilla s/n E-39008 Santander,		
Post Office Address: Same			
nventor's Signature	Date		

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: Miguel Molina Vila	Citizenship: Spain
Residence: Edificio 801A. Parque Tecnológico de Zamudio,	E-48160 Derio, Spain
Post Office Address: Same	
Inventor's Signature	Date

De:

Juan Arias [jarias@abgpatentes.com]

Enviado: martes, 07 de febrero de 2006 10:06

Para:

'Miguel Molina'; gvpqbp@iiqab.csic.es

CC:

gengbp@yahoo.es; 'Beatriz Rodera [ABG PATENTES]'

Asunto: RE: Contacto con Miguel Angel Molina

Estimado Sr. Molina:

Gracias por su e-mail.

En breve recibirá un e-mail de Beatriz Rodera (ABG patentes) en el que le detallará el motivo por el cual nos hemos puesto en contacto con usted (firma de un documento).

Reciba un saludo cordial

Juan Arias Sanz

Partner

M.Sc. (Chemistry)

Spanish Patent Agent / European

Patent Attorney

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Aviso de Confidencialidad

Este mensaje contiene información que puede ser CONFIDENCIAL y/o de USO RESTRINGIDO. Si usted no es el receptor deseado del mensaje (ni está autorizado a recibirlo por el remitente), no está autorizado a copiar, reenviar o divulgar el mensaje o su contenido. Si ha recibido este mensaje por error, por favor, notifiquenoslo inmediatamente y bórrelo de su sistema.

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Tel.: +34 91 417 1300

Fax: +34 91 417 1301

jarias@abgpatentes.com

http://www.abgpatentes.com

-----Mensaje original-----

De: Miguel Molina [mailto:miguelamol@hotmail.com] Enviado el: martes, 07 de febrero de 2006 9:32 Para: gvpqbp@iiqab.csic.es; jarias@abgpatentes.com

CC: gengbp@yahoo.es

Asunto: RE: Contacto con Miguel Angel Molina

Estimado Sr. Arias

A través de los Drs. Gregorio Valencia y Gemma Espuña me ha llegado la noticia de que deseaba vd. contactar conmigo. Puede encontrarme en esta dirección de correo electrónico.

Atentamente,

Miguel A Molina

From: Gregorio Valencia <qvpqbp@iiqab.csic.es>

To: jarias@abgpatentes.com

CC: miguelamol@hotmail.com, genqbp@yahoo.es

```
Subject: Contacto con Miguel Angel Molina
Date: Mon, 06 Feb 2006 18:42:48 +0100
>Sr. Juan Arias
>ABG Patentes
>Madrid
>Querido Juan,
>Efectivamente, como puedes ver en el mensaje, Gemma Espuña sigue en
>contacto con Miguel Angel Molina. En el encabezamiento del correo de
>respuesta de Gemma puedes encontrar la dirección de Miguel.
>Un abrazo, Gregorio
> >X-Original-To: gvpqbp@iiqab.csic.es
> > Delivered-To: gvpqbp@iiqab.csic.es
> > DomainKey-Signature: a=rsa-sha1; q=dns; c=nofws; s=s1024; d=yahoo.es;
> > h=Message-ID:Received:Date:From:Subject:To:In-Reply-To:MIME-Version:Content
> > -Type:Content-Transfer-Encoding;
> > b=J2OcTZeG07qq0ZpbNMz6f0dKRQU4U+D5yn9kzTmysPuV85T29QPTWR3o4rUIEYXx0Li5YuJM/
> > QIBUIrHNR1ZY4iBK+gADJ/xROI/B88uwADEkzXB8g6LFFBmOcUxHZr6yV8oUSESXFCKrpFHiQNd
> > Bgc0H9IxewObt1u2Krwlsuw= ;
> > Date: Sat, 4 Feb 2006 17:17:36 +0100 (CET)
> >From: Espuna Gemma <genqbp@yahoo.es>
> >Subject: RE: Vells temps
> >To: Gregorio Valencia <qvpqbp@iiqab.csic.es>,
> > Miguel Molina <miguelamol@hotmail.com>
> >X-imss-version: 2.031
> >X-imss-result: Passed
> >X-imss-scores: Clean:99.90000 C:2 M:3 S:5 R:5
> >X-imss-settings: Baseline:1 C:1 M:1 S:1 R:1 (0.0000 0.0000)
> >
                   Acabo de veure el teu missatge, perquè hem estat uns dies
> >Hola Gregori,
> >a Cinqueterre, canviant lleugerament d'aires i aprofitant per estirar les
> >cames. I tant que sé com localitzar en Miguel Ángel Molina, seguim en
> >contacte i fa poc que ens vam veure. També li envio una còpia d'aquest
> >missatge, o sigui que ja tens la seva adreça, així us podeu posar en
> > contacte entre vosaltres. Miguel, t'havia comentat que en Gregori
> > Valencia va ser el meu director de tesi al CSIC. Doncs mira, casualitats de
> >la vida...a veure quina sorpresa t'espera...esperem que sigui bona (encara
> >que vingui dels ex-col.legues d'allà dalt!). Molts petons a tots dos.
              P.D. Per cert, sembla que dilluns començaré una nova feina...a
> > Gemma
> > veure quant dura aquesta vegada...és el meu primer contracte indefinit, tot
> >i que no sé si vol dir gran cosa això...:-))
> > <> escribió:
> >Dra. Gemma Espuña
> >Estimade Gemma,
> >
> >M'acaba de trucar Juan Arias que és un patent officer que ens va redactar
> >les patents del diflunisal i el clioquinol. També ha redactat patent per
> >Med-Plant-Genetics. Et sona no?. Doncs ell sabia que nosaltres hi haviem
> >tingut una persona alli i per tant em demana si coneixem com es podria
> >localitzar a Miguel Angel Molina Vila. Esta a les teves mans?.
> >
> >Petons, Gregori
> >
> >NB. Ara mateix marxem a Zaragoza a un dels EPIs o sigui que fins dilluns no
> >et podré contestar
> >
> >
> >
```

Juan Arias

From: Laureano Simon [lsimon@progenika.com]

Sent: Wednesday, February 8, 2006 21:21 To: Beatriz Rodera [ABG PATENTES]

cc: Juan Arias

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear friends: Miguel Molina signed in his day, just like all the employees here in Progenika y Proteomika, myself included, a resign document in favor of Proteomika on any Intellectual Property generated by his work in the company. Additionally, this resign document also has an additional clause in his contract which was sent to Social Security.

I will send the contracts via fax.

Thanks.

Laureno

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Wednesday, February 8, 2006 11:00AM To: Laureno Simon" < lsimon@progenika.com > CC: Juan Arias < jarias@abgpatentes.com >

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Simon:

Regarding the patent application mentioned above, please find attached Mr. Molina's e-mail.

- Relating to the first question, we understand that there will be no problem with the address change, since he in no longer as Progenika Biopharma employee.
- Relating to the second question, we understand that we need to communicate Mr. Molina that if he signs the "Assignment" document he will lose any rights over the patent y that he will not receive any financial compensation.

The fact that we will have to inform Mr. Molina will lose any rights over the patent will make it difficult to get the documents signed by him; therefore, we can remind him of Article 15.1 of the patent law (11/1986) in which it cites the company as the only owner of the invention and also

```
Subject: Contacto con Miguel Angel Molina
Date: Mon, 06 Feb 2006 18:42:48 +0100
>Sr. Juan Arias
>ABG Patentes
>Madrid
>Querido Juan,
> Efectivamente, como puedes ver en el mensaje, Gemma Espuña sigue en
>contacto con Miguel Angel Molina. En el encabezamiento del correo de
>respuesta de Gemma puedes encontrar la dirección de Miguel.
>Un abrazo, Gregorio
>
> >X-Original-To: gvpqbp@iiqab.csic.es
> >Delivered-To: gvpqbp@iiqab.csic.es
> >DomainKey-Signature: a=rsa-sha1; q=dns; c=nofws; s=s1024; d=yahoo.es;
> > h=Message-ID:Received:Date:From:Subject:To:In-Reply-To:MIME-Version:Content
> > -Type:Content-Transfer-Encoding;
> > b=J2OcTZeG07qg0ZpbNMz6f0dKRQU4U+D5yn9kzTmysPuV85T29QPTWR3o4rUIEYXx0Li5YuJM/
> > OIBUIrHNR1ZY4iBK+qADJ/xROI/B88uwADEkzXB8g6LFFBmOcUxHZr6yV8oUSESXFCKrpFHiQNd
> > Bgc0H9IxewObt1u2Krwlsuw= ;
> >Date: Sat, 4 Feb 2006 17:17:36 +0100 (CET)
> >From: Espuna Gemma <genqbp@yahoo.es>
> >Subject: RE: Vells temps
> >To: Gregorio Valencia <gvpqbp@iiqab.csic.es>,
> > Miguel Molina <miguelamol@hotmail.com>
> >X-imss-version: 2.031
> >X-imss-result: Passed
> >X-imss-scores: Clean:99.90000 C:2 M:3 S:5 R:5
> >X-imss-settings: Baseline:1 C:1 M:1 S:1 R:1 (0.0000 0.0000)
> >
> >Hola Gregori,
                   Acabo de veure el teu missatge, perquè hem estat uns dies
> >a Cinqueterre, canviant lleugerament d'aires i aprofitant per estirar les
> > cames. I tant que sé com localitzar en Miguel Ángel Molina, seguim en
> >contacte i fa poc que ens vam veure. També li envio una còpia d'aquest
> >missatge, o sigui que ja tens la seva adreça, així us podeu posar en
> >contacte entre vosaltres. Miguel, t'havia comentat que en Gregori
> > Valencia va ser el meu director de tesi al CSIC. Doncs mira, casualitats de
> >la vida...a veure quina sorpresa t'espera...esperem que sigui bona (encara
> >que vingui dels ex-col.legues d'allà dalt!). Molts petons a tots dos.
> > Gemma P.D. Per cert, sembla que dilluns començaré una nova feina...a
> >veure quant dura aquesta vegada...és el meu primer contracte indefinit, tot
> > i que no sé si vol dir gran cosa això... :-))
> > <> escribió:
> > Dra. Gemma Espuña
> > Estimade Gemma,
> >
> >
> > M'acaba de trucar Juan Arias que és un patent officer que ens va redactar
> > les patents del diflunisal i el clioquinol. També ha redactat patent per
> >Med-Plant-Genetics. Et sona no?. Doncs ell sabia que nosaltres hi haviem
> >tingut una persona alli i per tant em demana si coneixem com es podria
> >localitzar a Miguel Angel Molina Vila. Esta a les teves mans?.
> >
> >Petons, Gregori
> >NB. Ara mateix marxem a Zaragoza a un dels EPIs o sigui que fins dilluns no
> >et podré contestar
> >
> >
 >
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Article 18.2 of the patent law (11/1986) in which the law cites that the employee needs to collaborate with the process.

Article 15.1 (11/1986) "The inventions made by the worker during the use of their contract or relation of work or services with the company, that are fruit of an activity of explicit or implicitly constituent investigation of the object of their contract, belong to the industrialist."

Article 18.2 (11/1986) "As much the industrialist as the worker will have their collaboration in the necessary measurement for the effectiveness of the rights recognized in the present Title, abstaining from any performance that can result in damage of such rights."

We look forward to further instructions, sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

From: Miguel Molina [malito:miguelamol@hotmail.com]

Sent: Wednesday, February 8, 2006 9:38

To: brodera@abgpatentes.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mrs. Rodera:

I have read the documents very closely; and some doubts which I would like to resolve before signing have come to my attention.

- The Patent Application shows Parque Tecnologico de Zamudio as my residency, when as you know, I do not work for Progenika (also before known as Proteomika)
- The Assignment documents states, that for ten dollars, "the applicants...transfer unto said assignee (Progenika) the full and exclusive right to the said invention:. Therefore, I understand that if the patent gets sold or if the application becomes commercial, the exclusive beneficiary would be Progenika, without me getting any kind of financial compensation.

Look to your response, sincerely,

Miguel A. Molina

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 16:10

To: miguelamol@hotmail.com

cc: Juan Arias (jarias@abgpatentes.com)

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

Thank you for your prompt response.

It will be sufficient if you could send us the documents via mail, or if possible certified, since we will need the documents to have your original signature as well as the original signature of a witness.

Greetings,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid

(SPAIN)

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Wednesday, February 8, 2006 11:00AM
To: Laureno Simon" < lsimon@progenika.com > CC: Juan Arias < jarias@abgpatentes.com >

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the

name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Simon:

Regarding the patent application mentioned above, please find attached Mr. Molina's e-mail.

- Relating to the first question, we understand that there will be no problem with the address change, since he in no longer as Progenika Biopharma employee.
- Relating to the second question, we understand that we need to communicate Mr. Molina that if he signs the "Assignment" document he will lose any rights over the patent y that he will not receive any financial compensation.

The fact that we will have to inform Mr. Molina will lose any rights over the patent will make it difficult to get the documents signed by him; therefore, we can remind him of Article 15.1 of the patent law (11/1986) in which it cites the company as the only owner of the invention and also Article 18.2 of the patent law (11/1986) in which the law cites that the employee needs to collaborate with the process.

Article 15.1 (11/1986) "The inventions made by the worker during the use of their contract or relation of work or services with the company, that are fruit of an activity of explicit or implicitly constituent investigation of the object of their contract, belong to the industrialist."

Article 18.2 (11/1986) "As much the industrialist as the worker will have their collaboration in the necessary measurement for the effectiveness of the rights recognized in the present Title, abstaining from any performance that can result in damage of such rights."

We look forward to further instructions, sincerely,

Beatriz Rodera Tobal Formalities Department

ABG PATENTES Phone: +34 91 417 1300

```
Subject: Contacto con Miguel Angel Molina
Date: Mon, 06 Feb 2006 18:42:48 +0100
>Sr. Juan Arias
>ABG Patentes
>Madrid
>Querido Juan,
>Efectivamente, como puedes ver en el mensaje, Gemma Espuña sigue en
>contacto con Miguel Angel Molina. En el encabezamiento del correo de
> respuesta de Gemma puedes encontrar la dirección de Miguel.
>Un abrazo, Gregorio
> >X-Original-To: gvpqbp@iiqab.csic.es
  >Delivered-To: gvpqbp@iiqab.csic.es
> > DomainKey-Signature: a=rsa-sha1; q=dns; c=nofws; s=s1024; d=yahoo.es;
> > h=Message-ID:Received:Date:From:Subject:To:In-Reply-To:MIME-Version:Content
> > -Type:Content-Transfer-Encoding;
> > b=J2OcTZeG07qg0ZpbNMz6f0dKRQU4U+D5yn9kzTmysPuV85T29QPTWR3o4rUIEYXx0Li5YuJM/
> > QIBUIrHNR1ZY4iBK+gADJ/xROI/B88uwADEkzXB8g6LFFBmOcUxHZr6yV8oUSESXFCKrpFHiQNd
> > Bqc0H9IxewObt1u2Krwlsuw= ;
> > Date: Sat, 4 Feb 2006 17:17:36 +0100 (CET)
> >From: Espuna Gemma <genqbp@yahoo.es>
> >Subject: RE: Vells temps
> >To: Gregorio Valencia <gvpqbp@iiqab.csic.es>,
> > Miguel Molina <miguelamol@hotmail.com>
> >X-imss-version: 2.031
> >X-imss-result: Passed
> >X-imss-scores: Clean:99.90000 C:2 M:3 S:5 R:5
> >X-imss-settings: Baseline:1 C:1 M:1 S:1 R:1 (0.0000 0.0000)
> >
                   Acabo de veure el teu missatge, perquè hem estat uns dies
> > Hola Gregori,
> >a Cinqueterre, canviant lleugerament d'aires i aprofitant per estirar les
             I tant que sé com localitzar en Miguel Ángel Molina, seguim en
'> >contacte i fa poc que ens vam veure. També li envio una còpia d'aquest
> >missatge, o sigui que ja tens la seva adreça, així us podeu posar en
> >contacte entre vosaltres. Miguel, t'havia comentat que en Gregori
> > Valencia va ser el meu director de tesi al CSIC. Doncs mira, casualitats de
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                                              Molts petons a tots dos.
> > que vinqui dels ex-col.legues d'allà dalt!).
               P.D. Per cert, sembla que dilluns començaré una nova feina...a
> > Gemma
> >veure quant dura aquesta vegada...és el meu primer contracte indefinit, tot
> >i que no sé si vol dir gran cosa això...:-))
> > <> escribió:
> > Dra. Gemma Espuña
> >Estimade Gemma,
> >
> >M'acaba de trucar Juan Arias que és un patent officer que ens va redactar
> >les patents del diflunisal i el clioquinol. També ha redactat patent per
> >Med-Plant-Genetics. Et sona no?. Doncs ell sabia que nosaltres hi haviem
> > tingut una persona alli i per tant em demana si coneixem com es podria
> >localitzar a Miguel Angel Molina Vila. Esta a les teves mans?.
> >
> >Petons, Gregori
> >NB. Ara mateix marxem a Zaragoza a un dels EPIs o sigui que fins dilluns no
> > et podré contestar
> >
> >
> >
```

Orense 68, 7a Planta 28020 Madrid (SPAIN) Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

From: Miguel Molina [malito:miguelamol@hotmail.com]

Sent: Wednesday, February 8, 2006 9:38

To: brodera@abgpatentes.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mrs. Rodera:

I have read the documents very closely; and some doubts which I would like to resolve before signing have come to my attention.

The Patent Application shows Parque Tecnologico de Zamudio as my residency, when as you know, I do not work for Progenika (also before known as Proteomika)

The Assignment documents states, that for ten dollars, "the applicants...transfer unto said assignee (Progenika) the full and exclusive right to the said invention:. Therefore, I understand that if the patent gets sold or if the application becomes commercial, the exclusive beneficiary would be Progenika, without me getting any kind of financial compensation.

Look to your response, sincerely,

Miguel A. Molina

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 16:10

To: miguelamol@hotmail.com

cc: Juan Arias (jarias@abgpatentes.com)

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

Thank you for your prompt response.

It will be sufficient if you could send us the documents via mail, or if possible certified, since we will need the documents to have your original signature as well as the original signature of a witness.

Greetings,

Beatriz Rodera TobalFormalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN)

From: Miguel Molina [malito:miguelamol@hotmail.com]

Sent: Wednesday, February 8, 2006 9:38

To: brodera@abgpatentes.com

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mrs. Rodera:

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- The Assignment documents states, that for ten dollars, "the applicants...transfer unto said assignee (Progenika) the full and exclusive right to the said invention:. Therefore, I understand that if the patent gets sold or if the application becomes commercial, the exclusive beneficiary would be Progenika, without me getting any kind of financial compensation.

Look to your response, sincerely,

Miguel A. Molina

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Tuesday, February 7, 2006 16:10

To: miguelamol@hotmail.com

cc: Juan Arias (jarias@abgpatentes.com)

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

Thank you for your prompt response.

It will be sufficient if you could send us the documents via mail, or if possible certified, since we will need the documents to have your original signature as well as the original signature of a witness.

Greetings,

Beatriz Rodera Tobal Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN)

Juan Arias

De:

Laureano Simon [Isimon@progenika.com]

Enviado: miércoles, 08 de febrero de 2006 21:21

Para:

Beatriz Rodera [ABG PATENTES]

CC:

Juan Arias

Asunto: Re: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimados amigos: Miguel Molina firmó en su día, como todos los empleados de Progenika y Proteomika, vo incluido, un documento de renuncia a favor de Proteomika sobre cualquie derecho de propiedad intelectual generada de su trabajo en la empresa. Y adicionalmente esta renuncia también figura como claúsula adicional en su contrato laboral enviado a la Seguridad Social Os envío por fax ambos contratos.

Gracias

Laureano.

---- Original Message -----

From: Beatriz Rodera [ABG PATENTES]

To: 'Laureano Simon'

Cc: Juan Arias

Sent: Wednesday, February 08, 2006 11:00 AM

Subject: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación a la solicitud de patente de la referencia, le adjuntamos el e-mail que nos ha escrito el Sr. Molina.

- Respecto a la primera pregunta que nos plantea, entendemos que no hay ningún problema en cambiar la dirección ya que no es trabajador de Progenika Biopharma, S.A.
- Respecto a la segunda cuestión, entendemos que debemos comunicarle que si firma el documento de "Assignment" perderá cualquier derecho sobre la invención y no recibirá ninguna compensación económica.

El hecho de comunicarle esta perdida de derechos dificultará la firma del documento por el inventor, por lo que podemos hacerle referencia a el Articulo 15.1 de la Ley de Patentes (11/1986) en el que se cita al empresario como propietario único de la invención y a el Artículo 18.2 de la Ley de Patentes (11/1986) en el se cita que el trabajador debe prestar su colaboración.

Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario"

Articulo 18.2 de la Ley de Patentes (11/1986) "Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

En espera de sus instrucciones, le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN) Tel.: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com http://www.abgpatentes.com

----Mensaje original----

De: Miguel Molina [mailto:miguelamol@hotmail.com] **Enviado el:** miércoles, 08 de febrero de 2006 9:38

Para: brodera@abgpatentes.com

Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera:

He leído atentamente los documentos que me envío, y se me han planteado un par de dudas más que me gustaría resolver antes de firmarlos

- -En la Patent Application se afirma que mi residencia es el Parque Tecnológico de Zamudio cuando, como usted ya sabrá, yo ya no trabajo para Progenika (antigua Proteomika)
- -En el Assignment of Patent Application se dice que, por diez dólares, "the applicants... transfer unto said asignee (Progenika) the full and exclusive right to the said invention". Por tanto, interpreto que si la patente se llegase a vender o tuviese alguna vez una aplicación comercial, el beneficiario exclusivo sería Progenika, sin que yo recibiese compensación económica alguna.

Esperando su respuesta, atentamente

Miguel A Molina

From: "Beatriz Rodera [ABG PATENTES]" < brodera@abgpatentes.com>

To: "Miguel Molina" <miguelamol@hotmail.com> CC: "Juan Arias" <jarias@abgpatentes.com>

Subject: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Date: Tue, 7 Feb 2006 16:09:41 +0100

Estimado Sr. Molina:

Muchas gracias por su rápida respuesta.

Será suficiente que nos lo mande por correo, a poder ser certificado, ya que necesitamos los documentos en los que aparezcan las firmas originales tanto de Vd. como de un testigo.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

De:

Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Enviado:

miércoles, 08 de febrero de 2006 11:01

Para:

'Laureano Simon'

CC:

Juan Arias (jarias@abgpatentes.com)

Asunto:

RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Importancia: Alta

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

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En espera de sus instrucciones, le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTESOrense 68, 7ª Planta
28020 Madrid

(SPAIN)

Tel.: +34 91 417 1300 Fax: +34 91 417 1301 <u>brodera@abgpatentes.com</u> http://www.abgpatentes.com

----Mensaje original-----

De: Miguel Molina [mailto:miguelamol@hotmail.com] **Enviado el:** miércoles, 08 de febrero de 2006 9:38

Para: brodera@abgpatentes.com

Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

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Esperando su respuesta, atentamente

Miguel A Molina

From: "Beatriz Rodera [ABG PATENTES]" < brodera@abgpatentes.com>

To: "Miguel Molina" < miguelamol@hotmail.com>

CC: "Juan Arias" < jarias@abgpatentes.com>

Subject: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Date: Tue, 7 Feb 2006 16:09:41 +0100

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Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN) Tel.: +34 91 417 1300 Fax: +34 91 417 1301

brodera@abgpatentes.com

http://www.abgpatentes.com

De:

Miguel Molina [miguelamol@hotmail.com]

Enviado: miércoles, 08 de febrero de 2006 9:38

Para:

brodera@abgpatentes.com

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Esperando su respuesta, atentamente

Miguel A Molina

From: "Beatriz Rodera [ABG PATENTES]" < brodera@abgpatentes.com>

To: "Miguel Molina" < miguelamol@hotmail.com>

CC: "Juan Arias" < jarias@abgpatentes.com>

Subject: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

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Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Tel.: +34 91 417 1300 Fax: +34 91 417 1301

brodera@abgpatentes.com http://www.abgpatentes.com

From: Juan Arias [jarias@abgpatentes.com] Sent: Thursday, February 9, 2006 15:30

To: 'Miguel Molina'

CC: Laureano Simon; Beatriz Rodera [ABG PATENTES]

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

In response to yesterday's e-mail, our comments are as follows:

- Relating to the address, there will be no difficulty in changing the address, since you are no longer a Progenika Biopharma employee.
- Relating to the question about the "Assignment" document, effectively, your signature will imply relinquishment of any right over the patent. Nevertheless, when you were employed with the company, you signed relinquishment to any right over Intellectual Property derived from work performed within the company, as it is stated in your work contract as well as it states in the resignation documents which are in favor of Proteomika, S.L. Please find attached both documents.

On the other hand, just as patent law (11/1986) established, inventions made by the worker during the use of their contract or relation of work or services with the company, belong to the industrialist and the worker has to collaborate in the necessary measurement for the effectiveness of the rights recognized in the present Title.

Article 15.1 (11/1986) "The inventions made by the worker during the use of their contract or relation of work or services with the company, that are fruit of an activity of explicit or implicitly constituent investigation of the object of their contract, belong to the industrialist."

Article 18.2 (11/1986) "As much the industrialist as the worker will have their collaboration in the necessary measurement for the effectiveness of the rights recognized in the present Title, abstaining from any performance that can result in damage of such rights."

Phone: +34 91 417 1300

Fax: +34 91 417 1301

We look forward to further instructions, sincerely,

Juan Arias
Partner
M.Sc (Chemistry)
Spanish Patent Agent/ European
Patent Attorney

ABG PATENTES
Orense 68, 7a Planta

28020 Madrid (SPAIN) brodera@abgpatentes.com www.abgpatentes.com

De:

Juan Arias [jarias@abgpatentes.com]

Enviado: jueves, 09 de febrero de 2006 15:30

Para:

'Miguel Molina'

CC:

'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'

Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Como respuesta a su e-mail de ayer le comentamos lo siguiente:

- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.
- En relación a la pregunta que nos hacía sobre la firma del documento de "Assignment", efectivamente la firma implica la renuncia a cualquier derecho sobre la invención. No obstante, cuando Vd. comenzó a trabajar en la empresa, firmó una renuncia a cualquier derecho sobre la propiedad intelectual derivada del trabajo que realizara dentro de la misma, tanto en su contrato de trabajo como en un documento de renuncia a favor de Proteomika, S.L. Le adjuntamos copia de ambos documentos.

Por otro lado, tal y como establece la Ley de Patentes (11/1986), las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario"

Articulo 18.2 de la Ley de Patentes (11/1986) "Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz

Partner

M.Sc. (Chemistry) Spanish Patent Agent / European Patent Attorney

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

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CONTRATO DE TRABAJO DE DURACION DETERMINADA

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Octava: El presente contrato se regulará por lo disp del Estatuto de los Trabajadores, por la Ley 12/2001	uesto en la legislación vigente que	months de este est de la	
del Estatulo de los Trabajadores, por la Ley 12/2001 de enero) y en su caso, por lo establecido en la Disp	l de 9 de julio (B.O.E. de 10 de juli	o). v Real Decreto 2 720/1998 de	tente por los artículos 12 y 15
desarrolla el citado art. 15 del Entatudo do los Teches	osición transitoria sexte del R.D.Le adores. Asimismo le será de anico	by 5/2002, de 24 de mayo (B.O.E.	de 25 de mayo), por el que se
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(13) Indiquese el nombre del trabajador sustituido			
(14) Solo para empresas de hasta 100 trabajadores y siempre	e quo tales acciones formativas estén fin	ancladas por cualquiera de las Administ	racionea Públicas (A.1. 1do laDis-
(15) Indicar el el puesto de trabajo a desampeñar será el de	Ilda la Imbajadorio o del electo de la la		
Igualmente deberá identificarse, en su caso, el puesto de (16) Indicar el porcentajo de reducción de la jornada y del sald	iño,èsia sará entre un 25 y un 85%.	Jucará tras el proceso de selección exter	na o promoción interna.

ACUERDO MUTUO DE CONFIDENCIALIDAD

El presente ACUERDO DE CONFIDENCIALIDAD (en adelante "Acuerdo") se formaliza a 27 de mayo de 2002.

REUNIDOS

- De una parte Laureano Simón Buela, con D.N.I. 35308166, Consejero Delegado de PROTEOMIKA, S.L. con domicilio a estos efectos en Joseph Samitier, 1-5, 08028 Barcelona, Barcelona, y C.I.F. B62793526 (cn adelante "Proteomika")
- De otra parte, Miguel Ángel Molina Vila con D.N.I. 33895291F con domicilio en Barcelona (en adelante "el trabajador").

EXPONEN

- Que PROTEOMIKA posee tanto información y tecnología confidencial relacionada con sus proyectos de I+D y los contratados por sus clientes como información relacionada con el negocio de PROTEOMIKA y sus empresas afiliadas incluyendo sin carácter limitativo, todos los datos comerciales y financieros así como también información relacionada de alguna forma.
- Que el trabajador ha sido contratado por la Empresa como Investigador con fecha 27 de Mayo de 2002
- 3. Que para la realización normal del trabajo, PROTEOMIKA va a revelar Información al trabajador en los términos y condiciones que se especifican en este acuerdo.

ACUERDAN

1. Interpretación

El objetivo del presente acuerdo:

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"Información de PROTEOMIKA": Incluye toda información propiedad de PROTEOMIKA sea cual sea su naturaleza, que dicha entidad considere que, por alguna u otra razón, no deba trascender a personas distintas de aquellas a quienes vaya estrictamente dirigida, incluyéndose en tal definición cualquier información, documentación y/o metodología desarrollada y/o elaborada por Proteomika desde su constitución así como la desarrollada y/o elaborada por las partes durante la vigencia del Contrato de Trabajo del Trabajador en la empresa.

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2. Compromisos

PROTEOMIKA se compromete:

1. a revelar al trabajador toda la información necesaria para la normal realización de las tareas relacionadas con su puesto de trabajo en la empresa.

El Trabajador se compromete:

- a utilizar toda la Información propiedad de PROTEOMIKA única y exclusivamente con el objeto de realizar las tarcas necesarias para el normal desempeño de su trabajo en la empresa;
- 2. a mantener la confidencialidad de la Información propiedad de PROTEOMIKA a la que tenga acceso sea cual sea la forma por la que el mismo haya tenido conocimiento de dicha información; y
- a devolver, todos los documentos y demás material en posesión custodia o control del trabajador, que contengan o incorporen parte de la Información propiedad de PROTEOMIKA, una vez que el trabajador deje de estar contratado por la empresa.

De conformidad con las obligaciones anteriores, el Trabajador no utilizará ni revelerá directa o indirectamente Información propiedad de PROTEOMIKA ni completa ni parcialmente excepto en lo pactado en este acuerdo.

3. Excepciones

- 3.1. Las anteriores restricciones impuestas a PROTEOMIKA no se aplicarán a Información propiedad del Trabajador que:
 - 3.1.1 el trabajador pueda probar que se encontraba en su posesión y a su libre disposición antes de la revelación efectuada por parte de PROTEOMIKA
 - 3.2.3 sea pública o pase a estar disponible al público, siempre que no sea mediante ni por culpa del trabajador.

Sin perjuicio de las restricciones establecidas a PROTEOMIKA y al Trabajador en el Artículo 2 del presente acuerdo, el Trabajador podrá revelar Información propiedad de PROTEOMIKA cuando tal revelación obedezca a un requerimiento o petición formal por parte de un Tribunal o cualquier otra autoridad gubernamental, siempre que previamente se le haya notificado tal petición a PROTEOMIKA y se le haya dado a la misma – si fuera posible- la oportunidad de oponerse a la necesidad de dicha revelación y/ o se le haya permitido solicitar una orden protectora o medida cautelar el objeto de que la Información revelada en virtud de esta petición, se utilice única y exclusivamente para el objeto para el que se dictó dicho requerimiento legal:

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4. Propiedad industrial

Todos los derechos de propiedad intelectual y/o industrial que se pudicran contener en la Información revelada o desarrollada por Proteomika desde su constitución, como la Información revelada o desarrollada durante el periodo en el que el trabajador es contratado por la empresa, son propiedad de PROTEOMIKA, y que en consecuencia el trabajador no tendrá derecho de naturaleza alguno sobre dicha Información revelada o desarrollada.

5. Daños y perjuicios

El contravenir este acuerdo deparará cuantas consecuencias preceptúe el ordenamiento jurídico así como cuantos daños y perjuicios pudiere inferir a Proteomika.

6. Duración del Acuerdo

Las condiciones del presente acuerdo serán vigentes durante el periodo de vigencia del contrato de trabajo en la empresa, y en el caso de que el trabajador abandonara la Empresa, un periodo de diez (10) años a partir de la fecha de cese del contrato de trabajo.

7. Ley aplicable

La validez, interpretación y cumplimiento del presente acuerdo se regirá por las leyes y normativa española aplicables a la misma.

8. Jurisdicción

Ambas partes contratantes, con renuncia a cualquier fuero propio que pueda corresponderles, se someten a la jurisdicción de los jucces y Tribunales de Barcelona para cualquier acción que pudiera derivarse de la interpretación o cumplimiento del presente contrato.

Y, en prueba de conformidad con cuanto antecede, ratificándose en todas y cada una de sus manifestaciones y estipulaciones, firman por duplicado y a un solo efecto el presente documento, en lugar y fecha "ut supra".

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Firma:

Nombre: Laureano Simón Buela Cargo: Consejero Delegado

En nombre y representación de

1.33

PROTEOMIKA, S.L.

Firma:

Nombre: Miguel Angel Molina Vila

PROGENIKA BIOPHARMA, S.A. Edificio 801 . Parque Tecnológico de Zamudlo 48160 Derío . Spain Phone: +34 94 406 45 25 Fax: +34 94 406 45 26



TO: JUAN ARIAS

For: LAVEAND SINEN

FRECEIVED

- 9 FEB. 2006

ASG Patentee, S.L.

Silve

SENDA BIOPHARIN SA . C.L. 3.452231



CONTRATO DE TRABAJO DE DURACION DETERMINADA

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Que reunen los requisitos exigidos para la celebración del presente contrato y, en consecuencia acuerdan formalizario con erregio a las siguientes:				
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Primera: La persona contratada prestará sus servicios como (3) el grupo profesional/categoría/nivel (4)		Investigadora	uvestigador.	incluido en
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(1) Padro, madre, tutor/a o persona o institución que le/la tenga a su cargo. (3) Indicar profesión.				
(4) Señalar el grupo profesional y la categoría o nivel profesional que correct	ponda, según el :	sistema de clasificació	eserome al ne elnopy tonoissiono no	
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Tercere: La duración del presente contrato se extenderá desde 27-05-03 haste 26-05-04 Se establece un período de prueba de (7) S/Estatuo Trabajadores En caso de que el convenio colectivo permita una duración mayor a la establecida legalmente, sefiálelo con una X:
Cuarta: El/la trebajador/a percibirá una retribución total de 28550 que se distribuye en los siguientes conceptos salariales (9)
que se distribuye en los siguientes conceptos salariales (9) Salario Base y Plus COnvenio
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Sexta: El contrato de duración determinada se celebra para;
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La realización de la obra o servicio (11)
Atender las exigencias circunstanciales del mercado, acumulación de tareas o exceso de pedidos, consistentes en
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por un plazo inferior a la duración máxima legal o convencionalmente establecida podrá promogarse, mediante acuerdo de las partes, por una única vez, sin que la duración total del contrato pueda exceder de dicha duración máxima.
Sustituir al trabajador (13), siendo la causa:
Sustituir a trabajadores con derecho a reserva del puesto de trabajo
Sustituir a trabajadoras por maternidad, sin bonificación de cuotas.
Sustituir a trabajadores excedentes por culdado de familiares, siendo el trabajador que sustituye al excedente, perceptor, durante más de un
a io, de prestationes por desempreo de ravel communito o asistencial (Disposición Adicional 14º del Real Decreto Legislativo 1/95).
Para cubrir temporalmente un puesto de trabajo durante el proceso de selección o promoción, para su cobertura definitiva.
Sustituir a trabajadores en formación por trabajadores beneficiarlos de prestaciones por desempleo (14). Se acompaña certificado expedido por la Administración Pública o entidad encargada de gestionar la formación.
El trabajador contratado desempeñará el puesto de trabajo de
Reducir la jornada de trabajo y el salario en un
les exigidas para tener derecho a la pensión contributiva de jubilación de la Segundad Social, con excepción de la edad, que habrá de ser inferior, como máximo, cinco años a la exigida, o cuando, reuniendo las citadas condiciones generales, hayan cumplido ya dicha edad.
Séptima: A la finalización del contrato, excepto en los casos de contrato de Interinidad, el trabajador tendrá derecho a recibir una indemnización de
cuantia equivalente a la parte proporcional de la cantidad que resultana de abonar ocho dias de salado por cada año de servicio, o la establecida, en
su caso, en la normativa específica que sea de aplicación.
Octava: El presente contrato se regulará por lo dispuesto en la legislación vigente que resulte de aplicación y particularmente por los articulos 12 y 15
US ESUBIDIO DE IOS ITADALADADES, DOFIA LEV 12/2011 OR XI OR INIO (M.C.) E. A. 10 A. INIO DE DANNE O 770 (4000 A.
UB BRIEFULY CO SU CASO, DOF IO BERRUIECIDO EN LA DISPOSICION IPROSICION SOVIO DO DE LOS EMPONOS. AA 24 da maria (D. O. C. da Or da maria)
desarrolla el citado art. 15 del Estatuto de los Trabajadores. Asimismo le será de aplicación lo dispuesto en el Convenio Colectivo de
Novena: El contenido del presente contrato se comunicará al Servicio Público de Empleo de
Dácima: Ambas partes se comprometen a comunicar el fin de la relación laboral a los Servicios Públicos de Empleo cuando esta se produzca, de conformidad con lo establecido en el artículo 42.3 de la Ley 51/1980, de 8 de octubre, Básica de Empleo.
CLÁUSULAS ADICIONALES
" El trabajudor renuncia a cualquier derecho sobre la propiedad intelectual derivado del trabajo a desarrollar en la Mercuntil contratante"
Y para que conste, se extiende este contreto por triplicado ejemplar, en el lugar y fecha a continuación Indicados, firmando las pertes interesadas. En
EVIa trabajador/a EVIa representante EVIa representante legal
de la primpresa del/de la menor, si procede
NO REPRESENTANTE
SINDICA
(7) Respetando lo establecido en el artículo 14.1 del Texto Refundidos de la Ley del Estatuto de los Trabajadores, aprobado por el Roal Docreto Legislativo 1/1995, de 24 de marzo.
(8) Diarios, semanales o mensuales.
(9) Salario base y complementos salariales (10) Mínimo: 30 días naturales.
(11) Identifique con claridad la obra o servicio, con autonomía y austantividad propia dentro de la actividad de la empresa en la que prestace servicio el trabajados contrabados
(15) Handrage is corea a corea francism as the francism of the
(13) Indiquese el nombre del trabajador sustituido. (14) Solo para empresas de hasta 100 trabajadores y stempre quo tales acciones formativas estén financiadas por cualquiera do las Administraciones Públicas (Art. 1do laDis-
(15) Indicar el el puesto do trabajo a desempeñar será el del/de la trabajador/a o del otro/a trabajador/a de la empresa que pase a desempeñar el puesto de aquel/equella. Igualmente deberá identificarse, en su caso, el puesto de trabajo cuya cobertura definitiva se producirá tras el proceso de selección externa o promoción interna.
(16) Indicar el porcentajo de reducción de la jornada y del salario, este será entre un 25 y un 85%.
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ACUERDO MUTUO DE CONFIDENCIALIDAD

El presente ACUERDO DE CONFIDENCIALIDAD (en adelante "Acuerdo") se formaliza a 27 de mayo de 2002.

REUNIDOS

- De una parte Laureano Simón Buela, con D.N.I. 35308166, Consejero Delegado de PROTEOMIKA, S.L. con domicilio a estos efectos en Joseph Samitier, 1-5, 08028 Barcelona, Barcelona, y C.I.F. B62793526 (en adelante "Proteomika")
- 2. De otra parte, Miguel Ángel Molina Vila con D.N.I. 33895291F con domicilio en Barcelona (en adelante "el trabajador").

EXPONEN

- Que PROTEOMIKA posee tanto información y tecnología confidencial relacionada con sus proyectos de I+D y los contratados por sus clientes como información relacionada con el negocio de PROTEOMIKA y sus empresas afiliadas incluyendo sin carácter limitativo, todos los datos comerciales y financieros así como también información relacionada de alguna forma.
- 2. Que el trabajador ha sido contratado por la Empresa como Investigador con fecha 27 de Mayo de 2002
- 3. Que para la realización normal del trabajo, PROTEOMIKA va a revelar Información al trabajador en los términos y condiciones que se especifican en este acuerdo.

ACUERDAN

1. Interpretación

El objetivo del presente acuerdo:

"Información de PROTEOMIKA": Incluye toda información propiedad de PROTEOMIKA sea cual sea su naturaleza, que dicha entidad considere que, por alguna u otra razón, no deba trascender a personas distintas de aquellas a quienes vaya estrictamente dirigida, incluyéndose en tal definición cualquier información, documentación y/o metodología desarrollada y/o elaborada por Proteomika desde su constitución así como la desarrollada y/o elaborada por las partes durante la vigencia del Contrato de Trabajo del Trabajador en la empresa.

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2. Compromisos

PROTEOMIKA se compromete:

 a revelar al trabajador toda la información necesaria para la normal realización de las tareas relacionadas con su puesto de trabajo en la empresa.

El Trabajador se compromete:

- a utilizar toda la Información propiedad de PROTEOMIKA única y exclusivamente con el objeto de realizar las tarcas necesarias para el normal desempeño de su trabajo en la empresa;
- 2. a mantener la confidencialidad de la Información propiedad de PROTEOMIKA a la que tenga acceso sea cual sea la forma por la que el mismo haya tenido conocimiento de dicha información; y
- 3. a devolver, todos los documentos y demás material en posesión custodia o control del trabajador, que contengan o incorporen parte de la Información propiedad de PROTEOMIKA, una vez que el trabajador deje de estar contratado por la empresa.

De conformidad con las obligaciones anteriores, el Trabajador no utilizará ni revelerá directa o indirectamente Información propiedad de PROTEOMIKA ni completa ni parcialmente excepto en lo pactado en este acuerdo.

3. Excepciones

- 3.1. Las anteriores restricciones impuestas a PROTEOMIKA no se aplicarán a Información propiedad del Trabajador que:
 - 3.1.1 el trabajador pueda probar que se encontraba en su posesión y a su libre disposición antes de la revelación efectuada por parte de PROTEOMIKA.
 - 3.2.3 sea pública o pase a estar disponible al público, siempre que no sea mediante ni por culpa del trabajador.

Sin perjuicio de las restricciones establecidas a PROTEOMIKA y al Trabajador en el Artículo 2 del presente acuerdo, el Trabajador podrá revelar Información propiedad de PROTEOMIKA cuando tal revelación obedezca a un requerimiento o petición formal por parte de un Tribunal o cualquier otra autoridad gubernamental, siempre que previamente se le haya notificado tal petición a PROTEOMIKA y se le haya dado a la misma – si fuera posible- la oportunidad de oponerse a la necesidad de dicha revelación y/ o se le haya permitido solicitar una orden protectora o medida cautelar el objeto de que la Información revelada en virtud de esta petición, se utilice única y exclusivamente para el objeto para el que se dictó dicho requerimiento legal.

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3.2.

4. Propiedad industrial

Todos los derechos de propiedad intelectual y/o industrial que se pudicran contener en la Información revelada o desarrollada por Proteomika desde su constitución, como la Información revelada o desarrollada durante el periodo en el que el trabajador es contratado por la empresa, son propiedad de PROTEOMIKA, y que en consecuencia el trabajador no tendrá derecho de naturaleza alguno sobre dicha Información revelada o desarrollada.

5. Danos y perjuicios

El contravenir este acuerdo deparará cuantas consecuencias preceptúe el ordenamiento juridico así como cuantos daños y perjuicios pudiere inferir a Proteomika.

6. Duración del Acuerdo

Las condiciones del presente acuerdo serán vigentes durante el periodo de vigencia del contrato de trabajo en la empresa, y en el caso de que el trabajador abandonara la Empresa, un período de diez (10) años a partir de la fecha de cese del contrato de trabajo.

7. Ley aplicable

La validez, interpretación y cumplimiento del presente acuerdo se regirá por las leyes y normativa española aplicables a la misma.

8. Jurisdicción

Ambas partes contratantes, con renuncia a cualquier fuero propio que pueda corresponderles, se someten a la jurisdicción de los jucces y Tribunales de Barcelona para cualquier acción que pudiera derivarse de la interpretación o cumplimiento del presente contrato.

Y, en prueba de conformidad con cuanto antecede, ratificándose en todas y cada una de sus manifestaciones y estipulaciones, firman por duplicado y a un solo efecto el presente documento, en lugar y fecha "ut supra".

Standard Special Science

Firma:

Nombre: Laureano Simón Buela Cargo: Consejero Delegado

En nombre y representación de

PROTEOMIKA, S.L.

Firma:

Nombre: Miguel Angel Molina Vila

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Wednesday, February 15, 2006 18:01

To: 'Miguel Molina'

CC: Laureano Simon; Juan Arias

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

We would like to remind you that we are still looking forward to your decision regarding the signing of the "Assignment" and "Declaration and Power of Attorney" documents sent on February 7, 2006.

We look forward to your response, sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid

(SPAIN)

Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

From: Juan Arias [jarias@abgpatentes.com] Sent: Thursday, February 9, 2006 15:30

To: 'Miguel Molina'

CC: Laureano Simon; Beatriz Rodera [ABG PATENTES]

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

In response to yesterday's e-mail, our comments are as follows:

- Relating to the address, there will be no difficulty in changing the address, since you are no longer a Progenika Biopharma employee.
- Relating to the question about the "Assignment" document, effectively, your signature will imply relinquishment of any right over the patent. Nevertheless, when you were employed with the company, you signed relinquishment to any right over Intellectual Property derived from work performed within the company, as it is stated in your work contract as well as it states in the resignation documents which are in favor of Proteomika, S.L. Please find attached both documents.

On the other hand, just as patent law (11/1986) established, inventions made by the worker during the use of their contract or relation of work or services with the company, belong to the industrialist and the worker has to collaborate in the necessary measurement for the effectiveness of the rights recognized in the present Title.

Article 15.1 (11/1986) "The inventions made by the worker during the use of their contract or relation of work or services with the company, that are fruit of an activity of explicit or implicitly constituent investigation of the object of their contract, belong to the industrialist."

Article 18.2 (11/1986) "As much the industrialist as the worker will have their collaboration in the necessary measurement for the effectiveness of the rights recognized in the present Title, abstaining from any performance that can result in damage of such rights."

We look forward to further instructions, sincerely,

Juan Arias
Partner
M.Sc (Chemistry)
Spanish Patent Agent/ European
Patent Attorney

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Enviado: miércoles, 15 de febrero de 2006 18:01

Para: 'Miguel Molina'

CC: 'Laureano Simon'; 'Juan Arias'

Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Le recordamos que estamos a la espera de que nos comunique su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" enviados con fecha 7 de febrero de 2006.

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7^a Planta 28020 Madrid (SPAIN) Tel.: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com

http://www.abgpatentes.com

----Mensaje original-----

De: Juan Arias [mailto:jarias@abgpatentes.com] **Enviado el:** jueves, 09 de febrero de 2006 15:30

Para: 'Miguel Molina'

CC: 'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'

Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Como respuesta a su e-mail de ayer le comentamos lo siguiente:

- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.
- En relación a la pregunta que nos hacía sobre la firma del documento de "Assignment", efectivamente la firma implica la renuncia a cualquier derecho sobre la invención. No obstante, cuando Vd. comenzó a trabajar en la empresa, firmó una renuncia a cualquier derecho sobre la propiedad intelectual derivada del trabajo que realizara dentro de la misma, tanto en su contrato de trabajo como en un documento de renuncia a favor de Proteomika, S.L. Le adjuntamos copia de ambos documentos.

Por otro lado, tal y como establece la Ley de Patentes (11/1986), las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario" Articulo 18.2 de la Ley de Patentes (11/1986) "Tanto el empresario como el

trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz Partner M.Sc. (Chemistry) Spanish Patent Agent / European Patent Attorney

ABG PATENTES

Orense 68, 7^a Planta 28020 Madrid (SPAIN)

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Este mensaje contiene información que puede ser CONFIDENCIAL y/o de USO RESTRINGIDO. Si usted no es el receptor deseado del mensaje (ni está autorizado a recibirlo por el remitente), no está autorizado a copiar, reenviar o divulgar el mensaje o su contenido. Si ha recibido este mensaje por error, por favor, notifiquenoslo inmediatamente y bórrelo de su sistema.

Tel.: +34 91 417 1300 Fax: +34 91 417 1301 jarias@abgpatentes.com

http://www.abgpatentes.com

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From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Monday, February 20, 2006 17:47

To: 'Miguel Molina'

CC: Laureano Simon; Juan Arias

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina,

We would really appreciate it if you could let us know of your decision regarding the signing of the "Assignment" and "Declaration and Power of Attorney" documents for the United States patent application.

Sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES
Orense 68, 7a Planta
28020 Madrid

(SPAIN)

Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Wednesday, February 15, 2006 18:01

To: 'Miguel Molina'

CC: Laureano Simon; Juan Arias

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

We would like to remind you that we are still looking forward to your decision regarding the signing of the "Assignment" and "Declaration and Power of Attorney" documents sent on February 7, 2006.

We look forward to your response, sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com From: Juan Arias [jarias@abgpatentes.com] Sent: Thursday, February 9, 2006 15:30

To: 'Miguel Molina'

CC: Laureano Simon; Beatriz Rodera [ABG PATENTES]

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

Dear Mr. Molina:

In response to yesterday's e-mail, our comments are as follows:

- Relating to the address, there will be no difficulty in changing the address, since you are no longer a Progenika Biopharma employee.

- Relating to the question about the "Assignment" document, effectively, your signature will imply relinquishment of any right over the patent. Nevertheless, when you were employed with the company, you signed relinquishment to any right over Intellectual Property derived from work performed within the company, as it is stated in your work contract as well as it states in the resignation documents which are in favor of Proteomika, S.L. Please find attached both documents.

On the other hand, just as patent law (11/1986) established, inventions made by the worker during the use of their contract or relation of work or services with the company, belong to the industrialist and the worker has to collaborate in the necessary measurement for the effectiveness of the rights recognized in the present Title.

Article 15.1 (11/1986) "The inventions made by the worker during the use of their contract or relation of work or services with the company, that are fruit of an activity of explicit or implicitly constituent investigation of the object of their contract, belong to the industrialist."

Article 18.2 (11/1986) "As much the industrialist as the worker will have their collaboration in the necessary measurement for the effectiveness of the rights recognized in the present Title, abstaining from any performance that can result in damage of such rights."

We look forward to further instructions, sincerely,

Juan Arias
Partner
M.Sc (Chemistry)
Spanish Patent Agent/ European
Patent Attorney

ABG PATENTES
Orense 68, 7a Planta
28020 Madrid
(SPAIN)

Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com

De:

Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Enviado: lunes, 20 de febrero de 2006 17:47

Para:

'Miquel Molina'

CC:

Juan Arias (jarias@abgpatentes.com); 'Laureano Simon'

Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608-N/Ref.: P1121USP@

Estimado Sr. Molina:

Estaríamos muy agradecidos nos comunicara su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" de la solicitud de patente en Estados Unidos.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Tel.: +34 91 417 1300 Fax: +34 91 417 1301

brodera@abgpatentes.com http://www.abgpatentes.com

----Mensaje original-----

De: Beatriz Rodera [ABG PATENTES] [mailto:brodera@abgpatentes.com]

Enviado el: miércoles, 15 de febrero de 2006 18:01

Para: 'Miguel Molina'

CC: 'Laureano Simon'; 'Juan Arias'

Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Le recordamos que estamos a la espera de que nos comunique su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" enviados con fecha 7 de febrero de 2006.

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Tel.: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com

http://www.abgpatentes.com

-----Mensaje original-----

De: Juan Arias [mailto:jarias@abgpatentes.com] Enviado el: jueves, 09 de febrero de 2006 15:30

Para: 'Miguel Molina'

CC: 'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'

Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Como respuesta a su e-mail de ayer le comentamos lo siguiente:

- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.
- En relación a la pregunta que nos hacía sobre la firma del documento de "Assignment", efectivamente la firma implica la renuncia a cualquier derecho sobre la invención. No obstante, cuando Vd. comenzó a trabajar en la empresa, firmó una renuncia a cualquier derecho sobre la propiedad intelectual derivada del trabajo que realizara dentro de la misma, tanto en su contrato de trabajo como en un documento de renuncia a favor de Proteomika, S.L. Le adjuntamos copia de ambos documentos.

Por otro lado, tal y como establece la Ley de Patentes (11/1986), las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario" Articulo 18.2 de la Ley de Patentes (11/1986) "Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz Partner

M.Sc. (Chemistry) Spanish Patent Agent / European Patent Attorney

ABG PATENTES

Orense 68, 7ª Planta 28020 Madrid (SPAIN)

Aviso de Confidencialidad

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Tel.: +34 91 417 1300 Fax: +34 91 417 1301

jarias@abgpatentes.com http://www.abgpatentes.com

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From: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Sent: Thursday, March 9, 2006 16:05

To: Miguel Molina [mailto: miguelamol@hotmail.com]

CC: Juan Arias < jarias@abgpatentes.com>, "Laureno Simon" < lsimon@progenika.com>

Subject: Patent Application in United States No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Subject: Patent Application in United States No. 10/550,608 Entitled: "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMNA, S.A.

Dear Mr. Molina:

Pursuant to our e-mail dated February 20, 2006, we forward the "Assignment" and "Declaration and Power of Attorney" documents once again accordingly they can be properly signed. In the "Declaration and Power of Attorney" documents we have left the address section blank in cases you would like to fill out your current address.

On the other hand, we have attached a copy of the application as it was filed before the United States Patent and Trademark Office. Also, we have forwarded a copy of the filing receipt which confirms the date of filing (September 26, 2006) as well as the serial number, 10/550,608.

Sincerely,

Beatriz Rodera Tobal

Formalities Department

ABG PATENTES Orense 68, 7a Planta 28020 Madrid (SPAIN) Phone: +34 91 417 1300 Fax: +34 91 417 1301 brodera@abgpatentes.com www.abgpatentes.com

De:

Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]

Enviado: jueves, 09 de marzo de 2006 16:05

Para:

'miquelamol@hotmail.com'

CC:

Juan Arias (jarias@abgpatentes.com); 'Laureano'

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Molina:

Como continuación a nuestro e-mail de fecha 20 de febrero de 2006, le remitimos de nuevo los documentos de "Assignment" y "Declaration and Power of Attorney" para que sean debidamente firmados. En el documento de "Declaration and Power of Attorney" hemos dejado en blanco el campo de su dirección para que si lo desea lo rellene con su actual dirección.

Por otro lado, le adjuntamos copia de la solicitud tal y como fue presentada ante la Oficina Norteamericana de Patentes (USPTO). También le remitimos copia de la notificación emitida por la USPTO en la que nos confirmaban la fecha de presentación (26 de septiembre de 2006) así como el número que le había correspondido, **10/550,608**.

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal

Formalities Department

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Assignment of Patent Application		
Whereas, we, Antonio Martínez Martínez, Laureano Simón Buela, Simón Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González, hereafter referred to as applicants, have invented certain new and useful improvements relating to an IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA [] for which an application for a United States patent was filed on, Application Number, and		
Whereas, PROGENIKA BIOPHARMA, S.A., herein referred to as assignee, whose post office address is Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª plantaE-48160 - DERIO - Vizcaya, Spain, is desirous of acquiring the entire right, title and interest in the same:		
Now, therefore, in consideration of the sum of ten dollars (\$10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.		
The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes. EXECUTED THIS day of, 20, at		
Antonio Martínez Martínez Date		
Witness		

Assignment of Patent Application			
Laureano Simón Buela	Date	<u> </u>	_
Witness			
Simón Santa Cruz	Date		_
Witness			
María Pilar Sáenz Jiménez	Date		_
Witness	•	<i>(</i>	
Corina Junquera Sánchez-Vallejo	Date		_
Witness			
José Javier Gómez Román	Date		_
Witness			
Jorge Cuevas González	Date		_
Witness			

	Assignment of Patent Application	
Miguel Molina Vila	Date	

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on ______ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: NO: X
Spain	P200300708	03/26/2003	YES: X NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	. FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Power of Attorney:	
As a named inventor, I hereby appoint the attorney(s) and/or	agent(s) under Customer Number 30868 to prosecute this
application and transact all business in the Patent and Trade	mark Office connected therewith.
Send correspondence to:	Direct telephone calls to:
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Kramer & Amado, P.C.	Arlir M. Amado
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I hereby declare that all statements made herein of my or information and belief are believed to be true; and further to willful false statements and the like so made are punishable by 18 of the United States Code and that such willful false stater patent issued thereon.	that these statements were made with the knowledge that y fine or imprisonment, or both, under Section 1001 of Title
Full Name of Inventor: Antonio Martínez Martínez	Citizenship: Spain
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Inventor's Signature	Date -
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Inventor's Signature	Date
involtor 3 Signature	
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Past Office Address: Same	

Inventor's Signature

Date

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DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: Miguel Molina Vila	Citizenship: Spain
Residence:	
Post Office Address: Same	•
Inventor's Signature	Date

Arty. Docket: ABG 3008 Today's Date: September 26, 2005
Applicants: Antonio Martínez Martínez, et al.

Serial No.: New

Filing Date: September 26, 2005
Title: IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

The following has been received in the U.S. Patent & Trademark Office on the dat stamped hereon:

- Transmittal Letter to the U.S. Designated/Elected Office Concerning Submission Under 35 U.S.C. 371 (2 pages)
- Credit Card Payment Form with Filing Fee of \$1530.00
- Application Data Sheet (6 pages)
- Patent Application including Claims 1-29, Figs. 1-5 and sequence listing (4 pages)
- Copy of PCT Application No. PCT/EP04/003219

Return to:

Arlir M. Amado KRAMER & AMADO, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Due Date: September 26, 2005

AMA/nsa

10/550608

JC06 Rec'd PCT/PTO 26 SEP 2005

Atty. Docket: ABG 3008 Today's Date: September 26, 2005

Applicants: Antonio Martínez Martínez, et al.

AMA/nsa

Serial No.: New
Filing Date: September 26, 2005

Title: IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

The following has been received in the U.S. Patent & Trademark Office on the date stamped hereon:

- Transmittal Letter to the U.S. Designated/Elected Office Concerning a Submission Under 35 U.S.C. 371 (2 pages)
- Credit Card Payment Form with Filing Fee of \$1530.00
- Application Data Sheet (6 pages)
- Patent Application including Claims 1-29, Figs. 1-5 and sequence listing (41
- Copy of PCT Application No. PCT/EP04/003219

Return to:

Arlir M. Amado KRAMER & AMADO, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Due Date: September 26, 2005

PTO-1390 (Rev. 02-2005)
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LICATION NO. (if known, see 37 CFR 1.5)
INTERNATIONAL ARRIVORTIONAL ARRIV

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) INTERNATIONAL APPLICATION NO. PCT/EP04/003219		ATTORNEY'S DOCKET NUMBER ABG 3008					
The following fees have been submitted			CALCULATIONS	PTO USE ONLY			
21.			\$ 300.00	1			
22.					\$ 200.00		
23. Search fee Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority					\$ 400.00		
TOTAL OF 21, 22 and 23 =			\$ 900.00				
Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is \$250 for each additional 50 sheets of paper or fraction thereof.							
Total Sheets	Extra Sheets		additional 50 or fraction to a whole number)	RATE			
- 100 =	/50 =			× \$250	\$		
Surcharge of \$130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(h)).					\$		
CLAIMS	CLAIMS NUMBER FILED NUMBER EXTRA RATE		RATE	\$			
Total claims	40	- 20 =	20	× \$50	\$ 1000.00	·	
Independent clain	ns 7	- 3 =	4	x \$200	\$ 800.00		
MULTIPLE DEPE	NDENT CLAIM(S) (if applicable)		+ \$360	\$ 360.00		
				CALCULATIONS =	\$ 3060.00		
Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by 1/2.							
SUBTOTAL =			\$ 1530.00				
Processing fee of \$130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)).			\$				
TOTAL NATIONAL FEE =			\$ 1530.00				
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +					\$		
TOTAL FEES ENCLOSED =					\$ 1530.00		
					Amount to be refunded:	\$	
					Amount to be charged:	\$	
a. A check in the amount of \$ to cover the above fees is enclosed.							
b. Please charge my Deposit Account No in the amount of \$ to cover the above fees. A duplicate copy of this sheet is enclosed.							
c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No50-0578 A duplicate copy of this sheet is enclosed.							
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NOTE: Where an	appropriate time	limit under 37 CF	R 1.495 has not been me		(37 CFR 1.137(a) or (b))	must be filed	
and granted to restore the International Application to pending status.							
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APPLICATION DATA SHEET

Application Information

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Filing Date:: 09/26/05

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Title:: IN VITRO METHOD TO DETECT BLADDER

TRANSITIONAL CELL CARCINOMA

Attorney Docket Number:: ABG 3008

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Suggested Drawing Figure:: None

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Application No.: New Attorney Docket No.: ABG 3008

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Representative Information

Representative Customer Number::	30868

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
·			

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

FIELD OF THE INVENTION

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The present invention refers to an *in vitro* method to detect the presence of a transitional cell carcinoma of the bladder in an individual, to determine the stage or severity of this cancer in the individual, or to monitor the effect of therapy administered to an individual with the said cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds for this cancer in an attempt to develop new medicinal products and to agents that inhibit expression and/or the activity of the FGFR3 protein.

BACKGROUND OF THE INVENTION

Despite all the advances that have been achieved during the last 20 years, cancer is still one of the leading causes of mortality worldwide. Transitional cell bladder cancer is the most common cancer of the urinary tract; it is also the fourth most common cancer in men and the eight most common in women. Based on data from the International Agency for the Investigation of Cancer, GLOBOCAN, for the year 2000, more than 136.000 new cases per year are diagnosed in Europe, 13.000 in Japan and 56.000 in North America. More than 3-4 times this number of patients are treated and monitored at hospitals every year; and more than 49.000, 4.500 and 12.000 deaths are due to bladder cancer every year in Europe, Japan and North America, respectively (according to the International Agency for Research on Cancer GLOBOCAN 2000).

Transitional cell carcinoma (TCC) is the most common type of *bladder cancer*, accounting for more than 90% of all cases. The remaining cases are squamous cell carcinomas (7%), adenocarcinomas (2%), and undifferentiated carcinomas (1%).

Tumour grade and stage are the best prognostic indicators of transitional cell carcinoma of the bladder. Bladder tumours are graded cytomorphologically from G1 to G3 in decreasing state of differentiation and increasing aggressiveness of the disease according to the World Health Organization (WHO). With respect to stage or invasivity, TCCs of the bladder are classified as superficial papillary (Ta and T1), muscle invasive (T2 to T4), or the uncommon carcinoma in situ or tumour in situ (TIS).

Low-grade (G1) tumours are usually confined to the mucosa or infiltrate superficial layers (stage Ta and T1). Most high-grade tumours are detected at least at T1 stage (invading lamina propria). Approximately 75% of the diagnosed bladder cancer cases are superficial. The remaining 25 % are muscle invasive at the moment of diagnosis.

transitional carcinoma including of the upper urinary tract, both *de novo* or in evaluating recurrence after treatment, including the detection of incipient invasive tumours or those at a high risk of developing aggressive disease.

Alteration of gene expression levels is tightly associated to uncontrolled cell growth and de-differentiation, common features of all cancers. The expression levels of the so-called "tumour suppressor genes", which act to block malignant cell growth, are repressed in tumour cells; and expression levels of the so-called "oncogenes", which act to induce malignant growth, are elevated in tumour cells.

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Many of these genes have been associated to bladder cancer development, including Rb, p53, p16, p14ARF, cyclin D1 (Fujimoto, K., et al., Cancer Res., 1998, 52:1393-1398; Grossman, B.H., et al., Clin. Cancer Res., 1998, 8:829-834; Balazs, M., et al., Genes Chromosomes Cancer, 1997, 19:84-89). The alteration in the expression of these genes could be used as a diagnostic marker of transitional cell carcinoma of the bladder; among these proposed markers have been proposed nuclear matrix protein NMP22 (Soloway, M.S., et al., J. Urol., 1996, 156:363-367; Casella, R., et al., J. Urol, 2000, 164:1926-1928), Hyaluronic Acid and Hyaluronidase (Pham, H.T., et al., Cancer Res., 1997, 57:778-783; Hautmann, S.H., et al., J. Urol., 2001, 165:2068-2074), Basement Membrane Complexes (BTA) (Pode, D., et al., J. Urol., 1999, 161:443-446; Thomas, L., et al., Clin. Chem. 1999, 45:472-477, Carcinoembryonic antigen (CEA) (Halim, A.B., et al., Int. J. Biol. Markers, 1992; 7:234-239), Uroplakin II (Wu, X.R., et al., Cancer Res.; 1998; 58:1291-1297), Scatter Factor/Hepatocyte Growth Factor (SF/HGF) (Gohji, K., et al., J. Clin. Oncol., 2000; 18:2963-2971), proteins of the keratin/cytokeratin family like cytokeratin 20 (Buchumensky, V., et al., J. Urol., 1998, 160:1971-1974), and cytokeratin 18 (Sánchez-Carbayo, M., et al., Clin. Cancer Res., 2000, 6:3585-3594), Mammary tumour 8-Ka Protein (MAT-8) (Morrison, B.W., et al., J. Biol. Chem., 1995, 270:2176-2182), Telomerase

However, it is likely that many of the genes involved in the initiation and progression of bladder cancer are currently unknown. No marker to predict the prognosis and extent of bladder cancer has been proven useful in clinical trials (Miyake et al., 2002). (Miyake, H., et al., J. Urol., 2002; 167:1282-1287). The identification of differentially expressed genes in bladder cell carcinoma could lead to the identification of biological markers, which could be of significant value for the diagnosis, prognosis and treatment of this disease.

Once transitional cell carcinoma of the bladder has been diagnosed, transurethral resection is carried out to treat superficial papillary tumours; superficial TIS and T1 are treated, in addition to transurethral resection, with intravesicular treatment with Bacillus-Calmette Guerin (BCG). If the cancer is muscle invasive, the patient is treated by radical cystectomy; if the patient will not tolerate this surgery, radiation therapy or chemotherapy is

19;20(32):4416-8; Dai et al. Anal Cell Pathol 2001;23(2):45-9) and in bladder carcinomas (Cappellen et al. Nat Genet 1999 Sep;23(1):18-20; Sibley et al. Oncogene 2001 Feb 8;20(6):686-91; Sibley et al. Oncogene 2001 Jul 19;20(32):4416-8; Billerey et al. Am J Pathol. 2001 Jun;158(6):1955-9) Activating FGFR3 mutations were detected in 40-50% of bladder tumours; the incidence was significantly higher, up to 80%, in low grade or superficial tumours than in high grade or invasive tumours; and the bladder cancer recurrence rates were clearly lower for tumours with a mutant FGFR3 (Kimura et al. Cancer 2001 Nov 15;92(10):2555-61; van Rhijn et al. Cancer Res 2001 Feb 15;61(4):1265-8).

Unexpectedly, the authors of the present invention have discovered, after thorough research and using different techniques, that the expression level of the FGFR3 gene and concentration of the protein is elevated in biopsies of bladder transitional cell carcinomas when compared with expression in normal bladder tissue and, moreover, the treatment of bladder cancer cell lines expressing high concentrations of FGFR3 with antibody against FGFR3 protein produce inhibition of cell proliferation of bladder cancer cell lines.

The authors of the present invention have also surprisingly discovered that the elevated levels of FGFR3 protein expression are predominantly associated with superficial tumours.

The present invention, therefore, provides a highly sensitive *in vitro* method to detect the presence of a bladder carcinoma, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with the said cancer. Also, the present invention provides targets or tools for the screening, identification, development and evaluation of the efficacy of therapeutic compounds for the treatment of cancer of the bladder, particularly for tumour treatment, as neoadjuvant before resection or as adjuvant after resection with the aim of reducing recurrence and progression. Finally, the invention provides agents characterised by the fact that they inhibit expression and/or activity of the FGFR3 protein for the treatment of cancer of the bladder.

SUMMARY OF THE INVENTION

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A first aspect of the present invention is to develop an *in vitro* method to detect the presence of cancer of the bladder, to determine the stage or severity of this cancer in the individual or to monitor the effect of the therapy administered to an individual with this cancer.

A second aspect of the present invention is an *in vitro* method to screen for, identify, develop and evaluate the efficacy of compounds to treat bladder transitional cell carcinoma.

An additional aspect of the invention lies in the use of sequences derived from the FGFR3 gene to establish the diagnosis and prognosis *in vitro* of bladder transitional cell

Figure 4 shows tissue array showing circular sections from bladder tissue biopsies after routine staining with hematoxylin and eosin followed by immunohistochemical staining for the FGFR3 protein.

Figure 5 shows immunohistochemical detection of FGFR3 protein in tissue samples of three stages of bladder transitional cell carcinoma, Ta (A and D), T1 (B), T2 (C) and control healthy bladder. Positive staining of FGFR3 was defined as a coarse cytoplasmic membrane reactivity. Immunohistochemistry was considered negative in cases with weak staining of <5% of the cells.

10 DETAILED DESCRIPTION OF THE INVENTION

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To facilitate the comprehension of the present patent application we give the meanings of some terms and expressions in the context of the invention:

The terms "subject" or "individual" refers to all species of animals classified as mammals and includes, but is not restricted to, domestic and farm animals, primates and humans. The subject is preferably a male or female human of any age or race

The term "cancer" refers to the disease that is typically characterised by abnormal or unregulated cell growth, capable of invading adjacent tissues and spreading to distant organs.

The term "carcinoma" refers to the tissue resulting from abnormal or unregulated cell growth.

The term "bladder transitional cell carcinoma" refers to any malign proliferative disorder in bladder epithelial cells.

The term "tumour" refers to any abnormal mass of tissue generated by a neoplastic process, whether this is benign (non cancerous) or malignant (cancerous).

The term "gene" refers to a region of a molecular chain of deoxyribonucleotides that encodes a protein and may represent a portion of a coding sequence or a complete coding sequence.

The term "DNA" refers to deoxyribonucleic acid. A DNA sequence is a sequence of deoxyribonucleotides.

The term "cDNA" refers to a nucleotide sequence complementary to a sequence of mRNA.

The term "RNA" refers to ribonucleic acid. An RNA sequence is a sequence of ribonucleotides.

The term "mRNA" refers to messenger ribonucleic acid, which is the fraction of total RNA, which translates to proteins.

polystyrene, polyvinylic alcohol and silicons. Examples of solid phase forms are the well of a plate or a purification column.

The terms "oligonucleotide primer" and "primer" are used interchangeably in the present invention, and are used to refer to nucleotide sequences, that are complementary to target nucleotide sequences of the FGFR3 or ribl10 genes. Each primer hybridises with its target nucleotide sequence and acts as an initiation site for nucleotide polymerisation catalysed by DNA polymerase, RNA polymerase or reverse transcriptase.

The term "probe", as it is used in the present invention, refers to a nucleotide sequence complementary to a nucleotide sequence derived from the FGFR3 gene that can be used to detect the corresponding nucleotide sequence derived from the FGFR3 gene.

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The term "therapeutic target" refers to nucleotide or peptide sequences against which a drug or therapeutic compound can be designed and clinically applied.

The term "antagonist" refers to any molecule that inhibits the biological activity of the antagonised molecule. Examples of antagonistic molecules include, among others, proteins, peptides, variations of natural peptide sequences and small organic molecules (with a molecular weight usually, but not limited to, less than 500 Daltons).

The present invention is based on the discovery that both gene expression of FGFR3, and the concentration of the FGFR3 protein are increased in bladder transitional cell carcinoma, and that the proliferation of bladder tumour cell lines is inhibited when they are treated with a specific antibody raised against the FGFR3 protein.

Therefore, the present invention first of all provides an *in vitro* method that comprises:

- the detection and/or quantification of the FGFR3 protein, of the mRNA of the FGFR3 gene, or of the corresponding cDNA in a sample of an individual, and
- b) the comparison of the amount of FGFR3 protein, of the mRNA of the FGFR3 gene or of the corresponding cDNA detected in a sample of an individual, with their normal reference values.

Said in vitro method is employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

The method provided by the present invention is highly sensitive and specific and is based on the fact that subjects or individuals diagnosed with bladder transitional cell carcinoma, present high levels of mRNA transcribed from the *FGFR3* gene (elevated levels of expression of the *FGFR3* gene) or elevated levels of the protein coded by the *FGFR3*

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used in these assays can be labelled or unlabelled; the unlabelled antibodies can be used in agglutination assays; the labelled antibodies can be used in a wide range of assays. Marker molecules that can be used to label antibodies include radionuclides, enzymes, fluorophores, chemoluminescent reagents, enzymatic substrates or cofactors, enzymatic inhibitors, particles, colorants and derivatives. There are a wide variety of assays well known to those skilled in the art that can be used in the present invention, which use unlabelled antibodies (primary antibody) and labelled antibodies (secondary antibodies); these techniques include but are not limited to the western-blot or western transfer, ELISA (Enzyme-Linked immunosorbent assay), RIA (Radioimmunoassay), Competitive EIA (Competitive enzyme immunoassay), DAS-ELISA (Double antibody sandwich-ELISA), immunocytochemical and immunohistochemical techniques, techniques based on the use of biochips or protein microarrays that include specific antibodies or colloidal precipitation in formats such as dipsticks. Other ways to detect and quantify the FGFR3 protein include affinity chromatography techniques, ligand binding assays or lectin binding assays. The preferred embodiment of this aspect of the invention is a double antibody sandwich ELISA (DAS-ELISA). In this immunoassay any antibody, or combination of antibodies can be used, that are specific against one or more epitopes of the FGFR3 protein. As an example of one of the many possible formats of this assay, a monoclonal or polyclonal antibody, or a fragment of this antibody, or a combination of these antibodies that recognise one or more epitopes of the FGFR3 protein are attached to the surface of a solid phase support and placed in contact with the sample to be analysed and incubated for a specific time and in appropriate conditions to form the antigen-antibody complexes. After washing in appropriate conditions to eliminate non-specific complexes, an indicator reagent, consisting in a monoclonal or polyclonal antibody, or a fragment of this antibody, or a combination of these and which recognises one or more epitopes of the target FGFR3 protein, bound to a signal generating molecule, is incubated with the antigen-antibody complexes in appropriate conditions of time and temperature. The presence of the FGFR3 protein in the sample to be analysed is detected and, if present, quantified and the signal generated is measured. The amount of FGFR3 protein present in the sample to be analysed is proportional to this signal.

When the aim is to detect and/or quantify mRNA or the cDNA corresponding to the FGFR3 gene and not the protein, the method of the invention to detect the susceptibility of an individual to develop transitional cell carcinoma of the bladder *in vitro* has several different steps. Hence, after obtaining the sample and extracting the total RNA, the method of the invention for the detection of the mRNA or of the corresponding cDNA of the FGFR3 gene, comprises a first step of amplification of the extract of total RNA or the corresponding cDNA synthesised by reverse transcription from the mRNA and a second step of

transfer and detecting it with specific RNA probes or of the corresponding cDNA of the *FGFR3* gene. In one specific embodiment of this aspect of the invention, amplification and quantification of the mRNA corresponding to the *FGFR3* gene, is carried out by quantitative RT-PCR in real time (Q-PCR).

The final step of the method of the invention to detect *in vitro* the presence of the cancer in a sample from an individual comprises comparing the amount of protein FGFR3, the amount of mRNA of the *FGFR3* gene or the amount of the corresponding cDNA, detected in a sample of an individual, with the amount of protein FGFR3, the amount of mRNA of the *FGFR3* gene, the amount of corresponding cDNA, detected in the samples of control subjects or in previous non-tumorous samples of the same individual or with normal reference values.

In another aspect, the invention also provides a method *in vitro* to identify and evaluate the efficacy of therapeutic agents against bladder transitional cell carcinoma that comprises:

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- a) placing into contact a culture of bladder tumour cells, with the candidate compound, in the appropriate conditions and for the time required for these to interact.
- detection and quantification of the expression levels of the FGFR3 gene or the FGFR3 protein or both, and

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c) comparing these expression levels with those of a control culture of tumour cells not treated with the candidate compound.

Quantification of the expression levels of the FGFR3 gene or the FGFR3 protein is performed in a similar manner to that described in the method of the invention to detect in vitro the presence of a cancer of the pancreas, especially of a bladder transitional cell carcinoma, in an individual.

When an agent reduces the expression levels of the FGFR3 gene or reverses the effects of high expression of this gene, preferably reducing the levels of cellular proliferation, this agent becomes a candidate for cancer therapy, in particular for bladder transitional call carcinoma.

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Another aspect of this invention refers to the use of nucleotide or peptide sequences derived from the *FGFR3* gene, in methods to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against bladder transitional cell carcinoma. It is noteworthy, the recent importance given to screening methods based on the competitive or non-competitive binding of the potential therapeutic molecule to the therapeutic target.

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A further aspect of this invention refers to the use of nucleotide or peptide sequences derived from the FGFR3 gene to detect the presence of a carcinoma, especially

determined from the sequence of the corresponding *FGFR3* gene by employing bioinformatic tools. The sequence of said primer pair is preferably selected from SEQ ID NO.1 and SEQ ID NO.2. These kits can be employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

The following examples serve to illustrate the invention.

Example 1.- Differential analysis of the expression of the FGFR3 gene in samples of bladder tissue, using *Human Genome U95 DNA arrays*

1.1. Materials and methods

Microarrays. GeneChip Test 3 (Affymetrix, Santa Clara) microarrays were used, that permit the quality of RNA to be tested before analysing expression with the GeneChip Human Genome U95A array (Affymetrix, Santa Clara), which represents 12,000 complete sequences of annotated genes; the FGFR3 gene is represented in the microarray by the set of probes 31805_at of Affymetrix, which are sense oligonucleotides 25 nucleotides long, designed on the basis of the Hs.1420 sequence of Unigene, or N. Acc. M64347 of GeneBank (Table 1).

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Table 1. Description of the probes corresponding to the set of probes 31805_at.

Consecutive order of probes	Region of the interrogated reference sequence	Probe sequence (5'-3')	Probe position in mRNA sequence	
1	3511	SEQ ID NO: 3	3227	
2	3625	SEQ ID NO: 4	3340	
3	3633	SEQ ID NO: 5	3348	
4	3663	SEQ ID NO: 6	3378	
5	3684	SEQ ID NO: 7	3399	
6	3716	SEQ ID NO: 8	3431	
7	3722	SEQ ID NO: 9	3437	
8	3821	SEQ ID NO: 10	3536	
.9	3825	SEQ ID NO: 11	3540	
10	3831	SEQ ID NO: 12	3546	
11	3861	SEQ ID NO: 13	3576	
12	3873	SEQ ID NO: 14	3588	
13	3891	SEQ ID NO: 15	3606	
14	3903	SEQ ID NO: 16	3618	
15	3933	SEQ ID NO: 17	3648	
16	4005	SEQ ID NO: 18	3720	

RNA was cleaned with the Rneasy kit (QIAGEN) (Chomczynski P. et al., Anal. Biochem., 1987, 162: 156; Chomczynski P., Biotechniques, 1993, 15: 532). Of each preparation of total RNA, 10 μg were used as starting material for synthesis of the first strand cDNA with the reverse transcriptase enzyme SuperScriptTM II RNase (Life Technologies), using as a primer an oligo-dT oligonucleotide carrying the T7 phage RNA polymerase promoter sequence. Second strand cDNA was synthesised using the enzymes DNA polymerase I of *E. coli* (Invitrogen Life Technologies), DNA ligase of *E. coli* (Invitrogen Life Technologies), RNAse H of *E. coli* (Invitrogen Life Technologies), and DNA polymerase of phage T4 (Invitrogen Life Technologies). The biotin labelled cRNA was synthesised using the ENZO BioArrayTM HighYieldTM Transcript Labelling Kit (Enzo Diagnostics Inc). After *in vitro* transcription, the unincorporated nucleotides were eliminated using the RNeasy columns (QIAGEN).

number of times that gene expression, is increased or decreased in the tumour sample compared to the non neoplastic control sample). We considered a SLR of 1 or -1 (representing respectively a fold change increase or decrease of 2) as a significant value for gene expression change

Compared to controls expression levels of *FGFR3* were increased more than 8-fold (SLR>3) in pTaG1 and pT1G3 carcinomas and more than 4-fold (SLR>2) in T2G3 carcinomas (Table 3).

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Table 3. Microarray hybridization results for Fibroblast growth factor receptor 3 (FGFR3) based on Affymetrix MAS5.0 software. (N. Acc. M64347)

Control	Control	Detection	SLR	TaG1	Comparison
sample	sample	pTaG1	TaG1 vs	Change	
signal	detection	stage	Control		
132.7	Р	Р	2.5	1	pTa.1 vs pC1
67.7	Α	Р	4.2	1	pTa.1 vs pC2
28.1	Α	Р	4.4	1	pTa.1 vs pC3
132.7	Р	Р	1	1 .	pTa.2 vs pC1
67.7	Α	P	3	I -	pTa.2 vs pC2
28.1	Α	P	3.5	1	pTa.2 vs pC3
SLR					
Average			3.1		
Control	Control	Detection	SLR	T1G3	Comparison
sample	sample	G3	T1G3 vs.	Change	
signal	detection	stage	Control		•
132.7	P	Р	1.7	i	pT1.1 vs. pC1
67.7	Α	Р	3.9	l	pT1.1 vs. pC2
28.1	Α	Р	3.7	I	pT1.1 vs. pC3
132.7	Р	Р	2	I	pT1.2 vs. pC1
67.7	A	P	4.1	ı	pT1.2 vs. pC2
28.1	Α	Р	4.4]	pT1.2 vs. pC3
SLR					
Average		·	3.3		
Control	Control	Detection	SLR	T2G3	Comparison
	ì	T2 G3	T2G3 vs		Companson
sample signal	sample detection	stage	Control	Citalige	
132.7	P	Р	1.4	1	pT2.1vspC1
67.7	A	P	3.3	Ī	pT2.1vspC2
28.1	A	P	3.2	<u> </u>	pT2.1vspC3
132.7	P	P	0.6	Ī	pT2.2vspC1
67.7	A	P	2.4	i	pT2.2vspC2
28.1	A	P	2.7	i	pT2.2vspC3
SLR		<u> </u>	-	·	TE
Average			2.26		

Cruz, CA, USA.) while the second membrane was probed with antibody raised against actin (Amersham, Little Chalfont, UK) as a control for protein loading. Finally, membranes were hybridised with a secondary antibody conjugated with peroxidase (Amersham) and the chemoluminescent signal was detected using the ECL system (Amersham) with high performance chemiluminescence film (Hyperfilm ECL, Amersham).

2.2. Results.

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Expression of the FGFR3 protein in bladder transitional cell carcinoma

FGFR3 protein expression in healthy samples (n = 3) and tumours (n = 15) was investigated by western blotting. The results are shown in figure 1 and table 4. As the results show the *FGFR3* protein was not detected in the control samples analysed. With regard to the tumour samples FGFR3 was present in 11 of the 15 samples analysed (73%), being higher in low-grade tumours (83%) and high-grade tumours that infiltrated the lamina propria (100%).

The receptor appeared in the form of several immunoreactive bands of distinct molecular weights: Western blot analysis showed bands forming a smear of glycosylated form 135 kDa, corresponding to the fully glycosylated form; 85 kDa corresponding to the intracellular non-glycosylated form and several bands of intermediate molecular weight corresponding with the different FGFR3 glycosylation states In addition some low molecular weight (50 kDa) immunoreactive bands were also present, which may represent proteolytic degradation products of the protein (Figure 1).

Table 4: FGFR-3 protein expression.

Sample	N	Samples	% Of samples	
		positive for	positive	
		FGFR3		
normal bladder	3	0	0	
TaG1	6	5	5 (83%)	
T1G3 Carcinoma	3	3	3 (100%)	
T2G3 Carcinoma	4	2	2 (50%)	
Unclassified	2	1	2 (100%)	

Amersham).

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Cell Proliferation Assays:

Experiments were performed to evaluate the effect of a mouse monoclonal antibody raised against human FGFR3 on the proliferation of RT-112 cells by comparing the proliferation rate of cells grown in the presence of the antibody raised against FGFR3 with proliferation in the presence of a control antibody raised against mouse \(\beta_2\)-microglobulin (Santa Cruz). The preservative sodium azide was first removed from the antibody solutions by washing and concentrating the antibodies three times with PBS using a 10-kDa Centricon filtration device (10-kDa MWCO, Millipore CO., Bedford, MA), followed by filter sterilization through a 0.2 µm filter previously saturated with Dulbecco's modified Eagle's medium (DMEM) and 10% FBS. Antibodies were diluted in culture media. RT-112 cells were seeded in a 96-well plate at a density of 2x10³ cells per well (0,2 ml) in RPMI medium containing 10% foetal bovine serum (FBS). Cells were allowed to attach to the wells for 24 hours before the RPMI medium was removed and replaced by fresh RPMI containing antibodies at concentrations of: 0, 0.02, 0.2, 2 and 20 µg/ml. The growth rate was estimated 24 and 48 hours by measuring the formation of reduced (methylthiazoltetrazolium) (Sigma Chemical Co., St Louis, USA) Briefly, after 1 and 2 days incubation, media was removed and replaced by 100 μl of 1 mg/ml MTT in RPMI medium containing 10% FBS. To provide the blanks for absorbance readings some control wells of medium alone were included. The plate was incubated for 30 to 60 minutes at 37°C. After the media was removed, 100 µl of DMSO were added to each well. The cells viability was determined by MTT absorbance (550 nm) and extrapolation of the absorbance intensity from a standard curve.

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3.2. Results.

Expression of FGFR3 protein in the bladder transitional cell carcinoma cell line RT-112:

Expression of FGFR3 was tested by western blot analysis, detecting high levels of the receptor (Figure 2). This appeared in the form of various immunoreactive bands of different molecular weights: 135 kDa corresponding to the fully glycosylated form; 85 kDa corresponding to the intracellular non-glycosylated form and several intermediate bands (100-110 kDa) corresponding to different FGFR3 glycosylation states. In addition lower molecular weight (50 kDa) immunoreactive bands were detected possibly corresponding to proteolytic degradation of the protein.

Example 4. Analysis of protein expression in tissue samples using tissue arrays

4.1. Material and Methods

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Fixed paraffin-embedded tumour samples from the pathology archives of the Hospital Universitario Marqués de Valdecilla were sectioned and arrayed on glass slides. In total 209 cases of urinary bladder transitional cell carcinoma from transurethral resection biopsies and cystectomy specimens and 20 healthy bladder samples (total: 229) were examined by immunohistochemical staining. All paraffin-embedded donor tissue blocks were sampled with 0.6-mm punchers using a Beecher tissue microarray instrument (Beecher Instruments Inc. Sun Prairie, WI, USA). Paraffin tissue array blocks containing arrayed core cylinders from 37 pTa, 100 pT1, 72 pT2 and 20 healthy bladder samples were subjected to routine staining with hematoxylin and eosin followed by immunohistochemical staining for the FGFR3 protein. A monoclonal antibody raised against FGFR3 (1:25 dilution; Santa Cruz Biotech. Inc., Santa Cruz, CA, USA) was used for immunostaining.

Briefly, antigen retrieval was performed by boiling sections in citric acid buffer in a pressure cooker for 90 sec. The Dako EnVisionTM + kit (Dako, Glostrup Denmark) was used as a visualization system according to the manufacturers' instructions, in a Techmate 500-220 automated immunostainer (Biotek, Santa Barbara, CA, USA). Diaminobenzidine was used as the chromogen (figure 4).

To reduce interobserver variability in the histopathological evaluation of the antibody-stained specimens three independent pathologists from the Pathological Anatomy Department of the University Hospital Marques de Valdecilla evaluated staining patterns and scoring criteria were agreed. Positive staining of FGFR3 was defined as a coarse cytoplasmic membrane reactivity (figure 5). Immunohistochemistry was considered negative in cases where staining was absent or which showed weak staining (<5% of cells in a given section).

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4.2. Results

Of the urinary bladder transitional cell carcinoma sections that were analysed immunohistochemically a positive reaction with the antibody specific for FGFR3 was positive in 71.4% of Ta sections, 72% of T1 sections and 49.2% of T2 sections (table 5) compared to the 5 % of healthy positive sample. Consistent with previous data the T1 sections

CLAIMS

1. An in vitro method that comprises:

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- a) the detection and/or quantification of the FGFR3 protein, of the mRNA of the FGFR3 gene, or of the corresponding cDNA in a sample of an individual, and
- b) the comparison of the amount of FGFR3 protein, of the mRNA of the FGFR3 gene or of the corresponding cDNA detected in a sample of an individual, with their normal reference values.
- 2. An *in vitro* method according to claim 1 which is employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.
- 3. Method according to claims 1 and 2 in which the sample to be analysed is a sample of bladder tissue.
 - 4. Method according to claim 3 in which the sample of bladder tissue is obtained by any conventional method, preferably by cystoscopy.
 - 5. Method according to claims 1 and 2 in which the sample to be analysed is a sample of urine, blood, plasma, pleural fluid, ascitic fluid, synovial fluid, bile, semen or cerebrospinal fluid.
- 6. Method according to claims 1 and 2 in which the sample to be analysed is obtained from an individual not previously diagnosed with bladder transitional cell carcinoma.
- 7. Method according to claims 1 and 2 in which the sample to be analysed is 30 obtained from an individual who has been previously diagnosed with bladder transitional cell carcinoma.
 - 8. Method according to claims 1 and 2 in which the sample to be analysed is obtained from an individual receiving treatment, or who has been treated previously against bladder transitional cell carcinoma.

- 15. Method according to claim 1 characterised in that the detection and/or quantification is done with specific probes either of mRNA or of the corresponding cDNA of the *FGFR3* gene, by techniques such as northern-blot or northern transfer.
- 16. Method according to claim 1 characterised in that the detection and/or quantification of the mRNA is done by Real time quantitative RT-PCR (Q-PCR).

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- 17. Use of nucleotide or peptide sequences derived from the *FGFR3* gene, to detect *in vitro* the presence of a bladder transitional cell carcinoma, to determine *in vitro* the stage or severity of this cancer in the individual, or to monitor *in vitro* the effect of the therapy administered to an individual with this cancer.
- 18. An *in vitro* method to identify and evaluate the efficacy of therapeutic compounds against cancer bladder transitional cell carcinoma that comprises:
 - a) placing in contact a culture of bladder tumour cells (with uncontrolled proliferation) with the candidate compound, in the appropriate conditions and for a suitable time for these to interact,
 - b) detect and/or quantifying expression levels of the FGFR3 gene or the FGFR3 protein, and
 - c) compare said expression levels with those of the control cultures of tumour cells not treated with the candidate compound.
- 19. Use of a nucleotide or peptide sequence derived from the FGFR3 gene, in methods to screen for, identify, develop and evaluate the efficiency of compounds to bladder transitional cell carcinoma.
 - 20. An agent that inhibits the expression and/or activity of the FGFR3 protein.
 - 21. An agent according to claim 20 selected from the group formed by:
 - a) an antibody, or combination of antibodies, specific against one or more epitopes present in the FGFR3 protein, preferably a human or humanised monoclonal antibody; a fragment of an antibody, a single chain antibody or an anti-idiotype antibody,
 - cytotoxic agents such as toxins, molecules with radioactive atoms or chemotherapeutic agents, including small organic and inorganic molecules, peptides, phosphopeptides, antisense molecules, ribozymes, triple helix

ABSTRACT

IN VITRO METHOD TO DETECT CARCINOMA BLADDER TRANSITIONAL CELL CARCINOMA

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The present invention refers to an *in vitro* method to detect a bladder transitional cell carcinoma, in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with this cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against this cancer in order to develop new medicinal products, and also agents that inhibit the expression and/or activity of the FGFR3 protein and/or the effects of this expression.

Figure 2

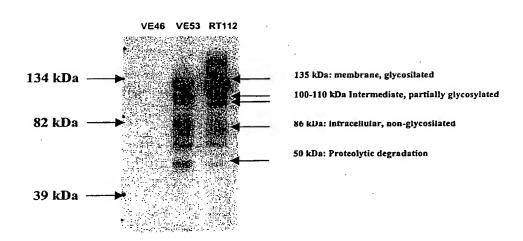
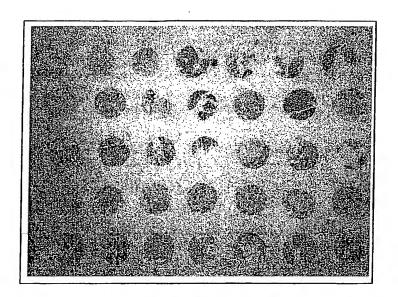


Figure 4



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